The American Journal of Medicine

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up to 500% greater absorption
80% less excretion
85% higher liver storage

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The American Journal of Medicine

VOL. X FEBRUARY, 1951 NO. 2

Editorial

Clinical Studies

Chronic beryllium granulomatosis, a major industrial hazard, was found in two cases to regress temporarily following ACTH therapy both subjectively and as indicated by careful laboratory evaluation. Similar improvement was also noted in a patient with silicosis. This experience is in accord with other reports of the favorable influence of ACTH on some patients with chronic pulmonary disease.

This study explores the effects of cortisone and ACTH in three patients suffering from chronic pulmonary insufficiency due chiefly to impairment of alveolar-capillary diffusion with respect to oxygen, now recognized as the mechanism of dyspnea common to a variety of diseases affecting the lungs. Two patients were markedly improved, one of these presenting a granulomatous lesion of the lungs without known exposure to beryllium, the other pulmonary disease of unknown etiology. A third patient with scleroderma involving the lungs was not benefited.

Dr. Galdston and his colleagues contribute a further study of the effects of ACTH in five patients with chronic lung disease, of whom two improved, two became worse due to retention of sodium and water, and one was unchanged. The observations include a careful analysis of the response to pulmonary function tests.

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practical ideals in diabetes

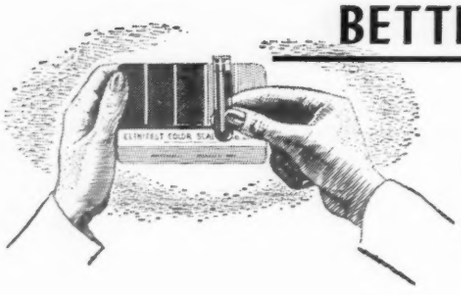
EARLY DIAGNOSIS

"The ideal detection center is in the private physician's office."[1] This approach to widespread early diagnosis of diabetes can be practical when *every routine examination of every patient includes urine-sugar analysis.* Routine analysis, in turn, is more practical for the physician who uses *Clinitest* (Brand) Reagent Tablets. The test is simple, rapid and self-contained (no external heating). Results are known at once

CLINITEST

REAGENT TABLETS ***for urine-sugar analysis***

BETTER CONTROL



"Generally, only the well controlled diabetic patient may expect to live to normal expectancy and without premature arterial degeneration."[2] Here too, practicality recommends *Clinitest*. The *Clinitest* (Brand) Urine-sugar Analysis Set (a compact pocket unit) enables the patient, under the physician's guidance, to make regular checkups simply, accurately and conveniently. This is a practical guarantee of the patient's cooperation without which adequate control by the doctor is hardly feasible.

Clinitest, reg. trademark

Bibliography: (1) Wilkerson, H. L. C.: New York State J. Med. *49*:2945 (Dec. 15) 1949. (2) Sweeney, J. S.: Texas State J. Med. *45*:623 (Sept.) 1949.

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Diagnostic Criteria of Vascular Headaches

		MIGRAINE	MIGRAINE EQUIVALENTS	MIGRAINE VARIANTS (e.g. Histaminic Cephalgia)	TENSION HEADACHE
BACKGROUND	INCIDENCE	8 to 10 million in U.S.; (ratio of women: men::2.5:1)	As common as migraine	Less common than migraine (mostly in men)	Most common of all headaches
	FAMILIAL HISTORY	Hereditary factor	Hereditary factor	Not significant	Not significant
ONSET OF ATTACK	STAGE OF LIFE	Puberty to menopause	Puberty to menopause	Often after 35	Any
	RATE OF ONSET	Abrupt to gradual	Abrupt to gradual	Abrupt	No pattern
	TIME OF DAY	Usually early morning, diminishing in evening	Variable	Frequent during sleep	Usually at end of day
	DAY OF WEEK, MONTH, ETC.	Most commonly weekends; frequently pre-menstrual and during periods of conflict, tension or stress.	Same as classical migraine	Occur in series, as often as 10 to 15 times a day, often seasonal.	Variable, but usually preceding or following emotional stress or conflict
DESCRIPTIVE QUALITIES OF HEADACHE	DURATION	Minutes to days	Minutes to days	Under 1 hour	No pattern
	NATURE OF HEAD PAIN	Throbbing or pulsating		Constant, boring	Sustained dull or sharp pain
	SITE	Anywhere in head and face—most commonly at right temple, usually unilateral	*SEE NOTE BELOW	Involves eye, neck and often face; unilateral	Most intense in neck, shoulders and occiput — may spread to frontal region—unilateral or bilateral
	TENDERNESS (RESIDUAL)	Near large extra-cranial arteries. Affected region may involve nasal, paranasal, teeth, ear, neck.	Varies according to location	No residual tenderness	Any of head and neck muscles
	EFFECT OF MANUAL PRESSURE	Pressure upon temporal, frontal, post-auricular arteries often reduces intensity	*NOTE Many cases in this classification suffer pain in regions other than the head	Similar to migraine (classical)	Pressure upon tender muscles or regions of tenderness intensifies headache
	EFFECT OF POSITION OF HEAD	Erect position relieves—shaking head aggravates		Pain eased by sitting up and leaning forward	Shaking head reduces intensity by extending muscles
ASSOCIATED SYMPTOMS OF ATTACK	VISUAL DISTURBANCES	Scintillating scotomata; unilateral homonymous hemianopia usually of short duration preceding attack. Photophobia common	Same as classical migraine Photophobia always present in ophthalmic migraine	Photophobia often present	Partial closure of eyes due to muscle spasm. May give impression of faulty vision; Photophobia common
	OTHER OCULAR SYMPTOMS	Injection of conjunctiva and sclera, lacrimation and ptosis of eyelid may occur	Ptosis of eyelid occurs with ophthalmoplegic migraine	Conjunctival injection, lacrimation, nasal stuffiness, discharge	Injection of sclera and conjunctiva; lacrimation may also occur
	VERTIGO AND OTHER SENSORY DISTURBANCES	May be present; paresthesias of hands and face may precede	Paresthesias of hands and face may precede	Infrequent	Infrequent
	MOOD CHANGES	Depression-irritability precede; exaltation follows	Same as classical migraine	No significant changes	Tension, irritability; desire for attention
	GASTRO-INTESTINAL DISTURBANCES	Anorexia, nausea and vomiting at height of attack; flatulence and distension	In gastro-intestinal migraine - flatulence, distension, constipation	Infrequent	Flatulence and distension common especially with severe headache
	CHANGE IN BODY TEMPERATURE	Slight; sometimes unilateral sweating	In some cases up to 104°F.	Not significant	Chills and hot flashes without change in temperature
	TREATMENT	Emotional guidance, general improvement in health; Endocrine therapy. Specific for attack: Cafergot	Emotional guidance, general improvement in health; Specific for attack: Cafergot; vaso-constrictor agent		Sedatives

The information presented in this table has been compiled by the Sandoz Scientific and Research Staffs from the following publications:

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Sandoz Pharmaceuticals

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68 CHARLTON STREET, NEW YORK 14, NEW YORK

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Case Reports

leading a normal life...

The patient with coronary disease—angina pectoris or congestive heart failure can count on resuming nearly all normal activities when placed on Theobarb medication. Theobarb provides the marked coronary vasodilatation, enhanced cardiac output and sustained diuresis of theobromine plus the tranquilizing effect of phenobarbital... with the lowest incidence of disturbing side reactions.

The therapeutic value of Theobarb (theobromine plus phenobarbital) is extended in the following Theobarb Combinations:

Theobarb with Mannitol Hexanitrate—Theobarb Special with Mannitol Hexanitrate—Theobarb with Rutin—Theobarb with Ephedrine.

Supplied in bottles of 50 and 500 tablets.

Each Theobarb tablet contains:

Phenobarbital	½ gr.
Theobromine	5 gr.

Dosage: 1 to 4 tablets daily, preferably during or immediately after meals.

Supplied in bottles of 50 and 500 tablets.

Also available as Theobarb Special, each tablet containing Phenobarbital, ¼ gr. and Theobromine, 5 gr.

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a practical *step forward* in the therapy of rheumatic affections

Pabalate usually provides better therapy for rheumatic affections than pure salicylate itself, through its mutually synergistic combination of para-aminobenzoic acid and salicylate.[1,2] Reports of authoritative clinical tests show a *higher* degree of pain relief... to *more* patients... on *lower* dosage... over *longer* periods... with *greater freedom* from adverse reactions.[3]

REFERENCES: 1. Dry, T. J. et al.: Proc. Staff Meetings Mayo Clin., 21:497, 1946. 2. Hoagland, R. J.: Am. J. Med., 9:272, 1950. 3. Smith, R. T.: J. Lancet, 70:192, 1950.

FORMULA: Each enteric-coated tablet or each teaspoonful of chocolate-flavored liquid contains 0.3 Gm. (5 gr.) sodium salicylate U.S.P., and 0.3 Gm. (5 gr.) para-aminobenzoic acid (as the sodium salt).

A. H. ROBINS CO., INC.
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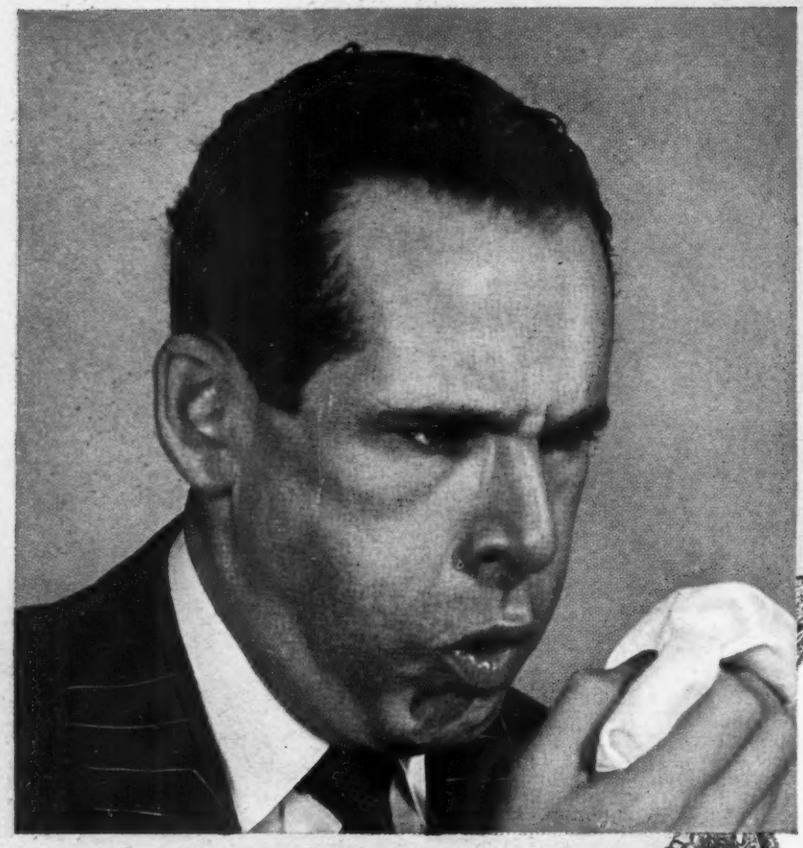
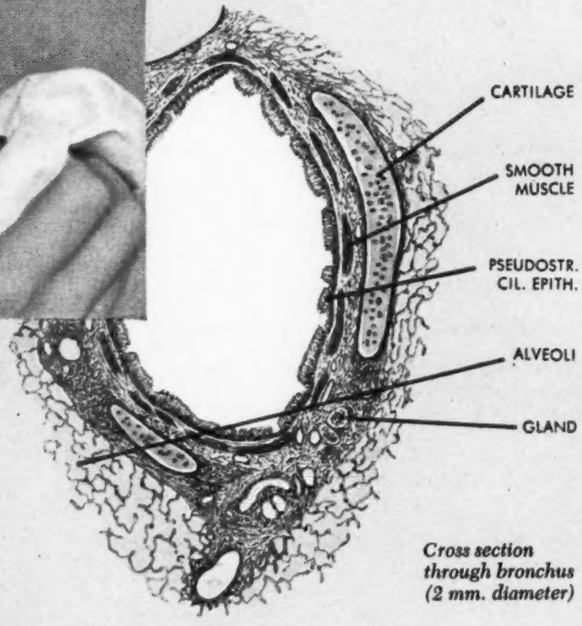
Robins **Pabalate®**

Seven Years' Research that opened a **New Era**

in Cough Therapy





Cross section through bronchus (2 mm. diameter)

The time encrusted *empirical* approach to cough therapy—with its "picture of confusion, contradiction and neglect"[2]—can now be replaced by sound, *rational* non-narcotic treatment, thanks to the pioneering studies of Boyd et al.,[1,2] demonstrating that glyceryl guaiacolate is the most powerful of expectorants commonly used. Robitussin—the antitussive-expectorant with specific drug action—provides glyceryl guaiacolate for increasing respiratory tract fluid, together with desoxyephedrine, for its bronchial-spasm-relieving[3] and its mood-improving actions—in an aromatic syrup that is highly patient-acceptable.

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promotes useful cough...
minimizes harmful cough

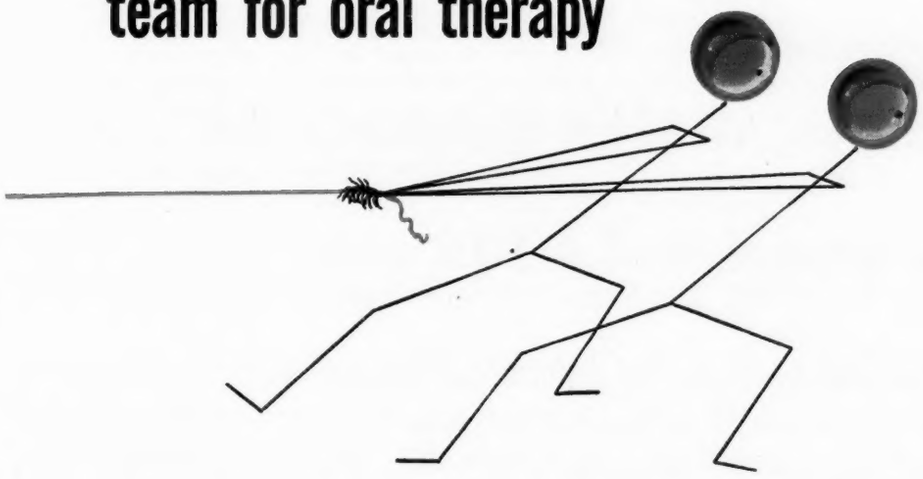
References:

1. Boyd, E. M. and Lapp, S.: J. Pharmacol. and Exper. Therap., 87:24, 1946. 2. Connell, W. F. et al.: Canad. M.A.J., 42:220, 1940. 3. Novelli, A. and Tainter, M. L.: J. Pharmacol., 77:324, 1943.

Formula:

Each 5 cc. (1 teaspoonful) contains 100 mg. glyceryl guaiacolate and 1 mg. desoxyephedrine hydrochloride, in a palatable aromatic syrup.

team for oral therapy



The daily administration of one or two Tablets MERCUHYDRIN® with Ascorbic Acid usually produces adequate diuresis in the cardiac patient whose water and electrolyte balance *has already been stabilized by parenteral mercurial diuretic therapy.* At this stage, the edema-free state – manifested by the unfluctuating basic weight – can be maintained with the tablets, either alone or supplemented by injections at appropriate intervals.

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...but the patient too seldom appreciates... that

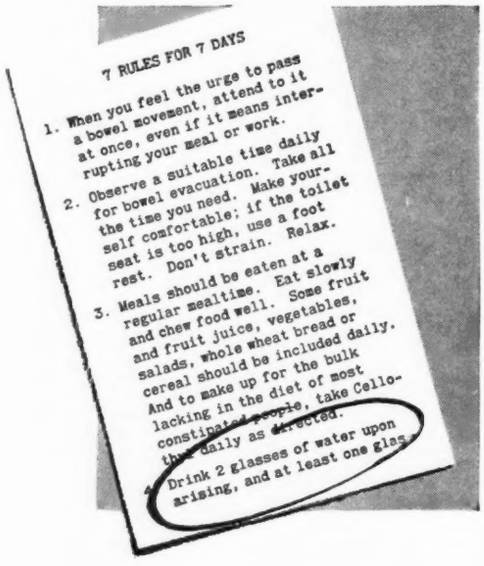
a normal stool is 80% water[1]

The physiologic role of water in constipation correction is evident: the presence of adequate water is necessary to stimulate gastric action, facilitate intestinal absorption, and assure comfortable, easily passed stools of good caliber and consistency.

An aid to patient-education:

Sufficient water intake is advised in "7 Rules for 7 Days," a simple leaflet designed to help the patient understand and overcome the "improper habits of living and eating"[2] which cause constipation.

Available to physicians: Pads of the "7 Rules" may be had on request. Simply write "7 Rules" on a prescription blank and send to Chilcott Laboratories, Morris Plains, New Jersey.


7 RULES FOR 7 DAYS

1. When you feel the urge to pass a bowel movement, attend to it at once, even if it means interrupting your meal or work.
2. Observe a suitable time daily for bowel evacuation. Take all the time you need. Make yourself comfortable; if the toilet seat is too high, use a foot rest. Don't strain. Relax.
3. Meals should be eaten at a regular mealtime. Eat slowly and chew food well. Some fruit and fruit juice, vegetables, salads, whole wheat bread or cereal should be included daily. And to make up for the bulk lacking in the diet of most constipated people, take Cellothyl daily as directed.
4. Drink 2 glasses of water upon arising, and at least one glas

An aid to physiologic correction:

Cellothyl, physiologically correct bulk, may be prescribed (with adequate water) for improved bowel function.

Constipation correction in the physiologic manner

Some authorities have observed that adequate water intake, plus proper diet, will produce regular daily bowel movements without adjuvant medication. However, more recent investigations prove the value of adding Cellothyl (physiologically correct hydrophilic colloid) to a well-ordered anticonstipation program. In fact, 80 to 92% of patients treated in private practice obtained "good" to "excellent" results with Cellothyl[3, 4]—and in obstinate clinic-treated cases[2] it was found that even years of constipation can be corrected in days with Cellothyl.

Physiologic constipation correction and *patient-understanding*

A combination of therapeutic regimen and patient-cooperation offers the most effective constipation correction. Explanation of the "simple rules of bowel hygiene"[4] helps the patient understand the importance of sufficient daily water intake, proper diet, regular meals, etc. – good habits so essential for normal bowel function. The leaflets "7 Rules for 7 Days" outline a simple patient-program—easy to follow and physiologically correct. Pads for office use are available on request.

Physiologic constipation correction and *Cellothyl*

When the usual program of diet-and-instruction per se fails to alter deeply ingrained habits, Cellothyl acts to correct constipation in a physiologic manner: following the normal digestive gradient, Cellothyl passes through the stomach and small intestine in a fluid state, then thickens to a smooth gel in the colon to furnish bulk – where bulk is needed – for soft, moist, well-formed stools.

To facilitate hydrophilic action, "the intake of adequate amounts of fluids, at least 2.5 to 3.5 liters daily, is of the greatest importance."[2] *Each dose of Cellothyl must be taken with a full glass of water.* When properly used in adjunct to any well-planned anticonstipation regimen, Cellothyl may help to achieve more normal bowel habits "in the course of a few days."[5]

Dosage: 3 Tablets t.i.d. until normal stools pass regularly. Continue at minimum level for as long as required. *Daily fluid intake must be high.*

In *"cathartic addiction,"* administer for several days ½ the usual dose of cathartic together with Cellothyl, then ¼ the usual dose, then Cellothyl alone for as long as necessary. Cellothyl is not habit-forming.

Because Cellothyl acts in an unhurried, physiologic manner, time must be allowed for it to pass through the digestive tract into the colon and rectum.

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1. Gray, H. and Tainter, M. L.: Am. J. Digest. Dis. 8:130, 1941.
2. Bargen, J. A.: Gastroenterology 13:275, 1949.
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4. Schweig, K.: New York State J. Med. 48:1822, 1948.
5. Council on Pharmacy and Chemistry: J.A.M.A. 143:897, 1950.

Are you using the "7 Rules" for constipation correction?

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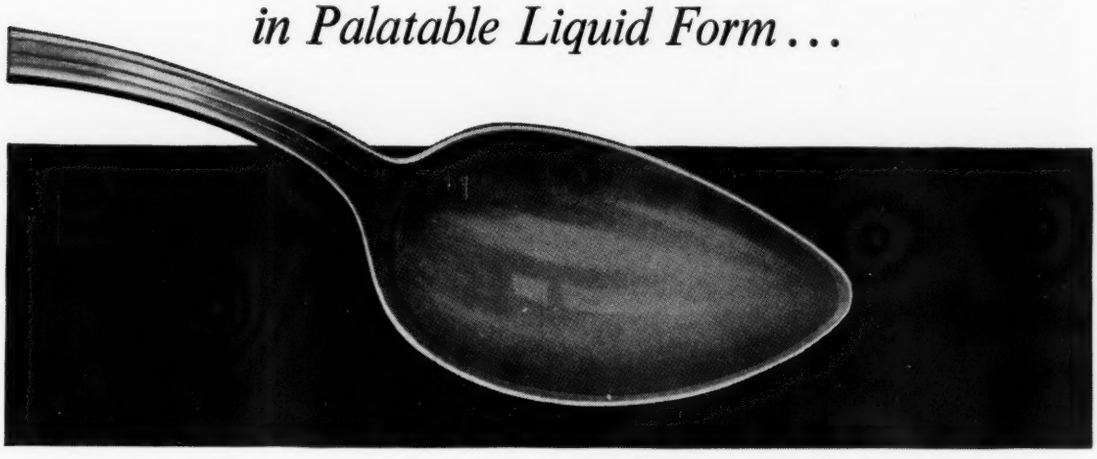

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—in pleasant-tasting, convenient liquid form, readily acceptable to infants, children, adults.

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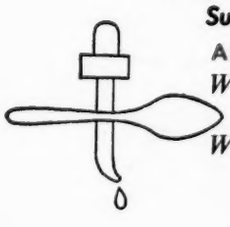

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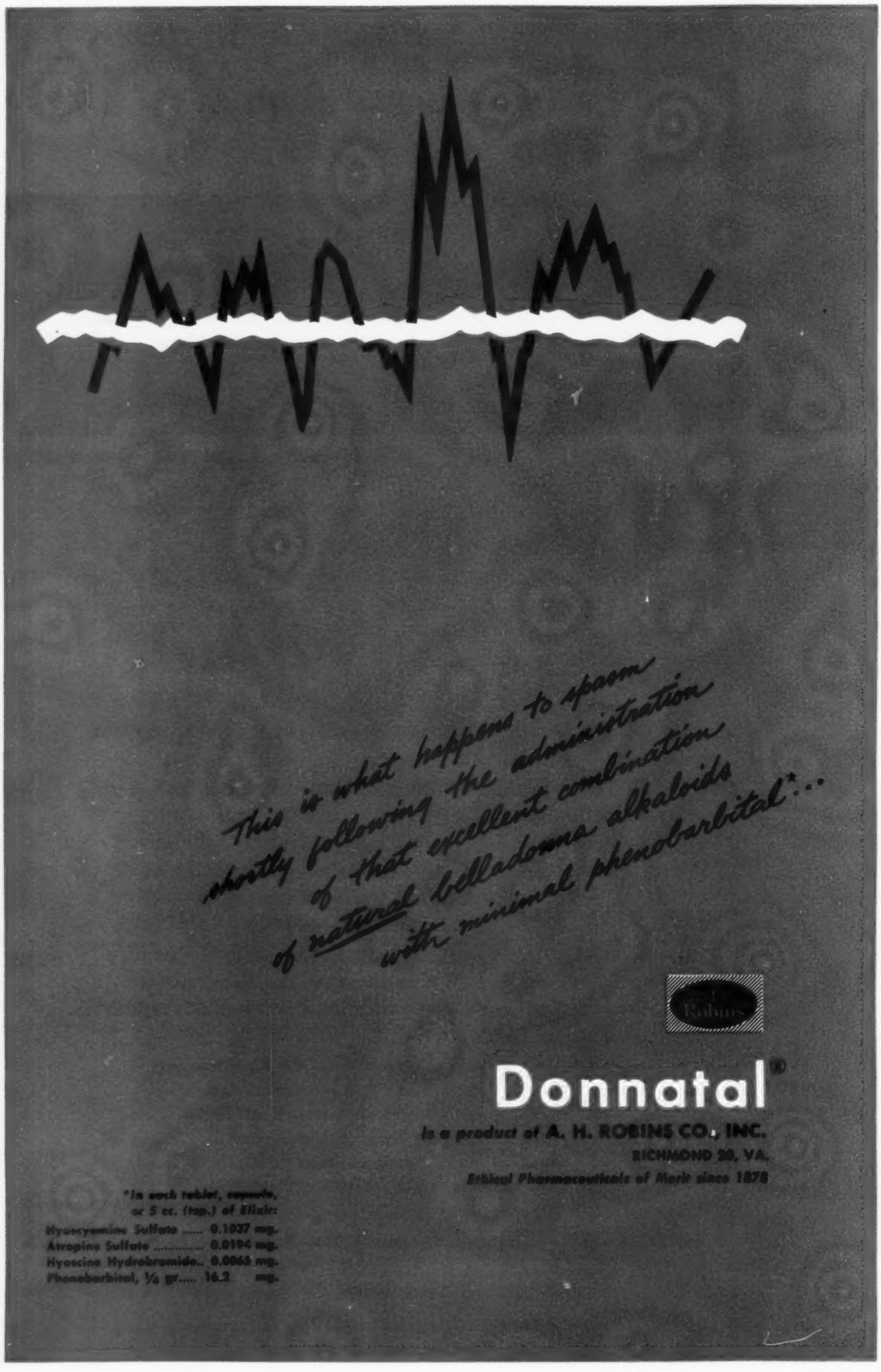
1. Keefer, C. S.: Amer. J. Med. 7:216 (1948).
2. Kolmer, J. A.: Amer. J. Med. Sc. *215*:136 (1948).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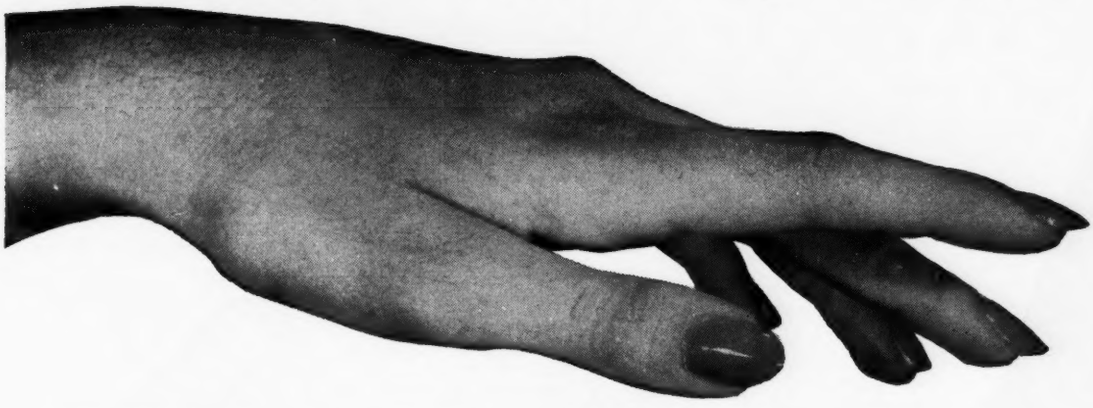

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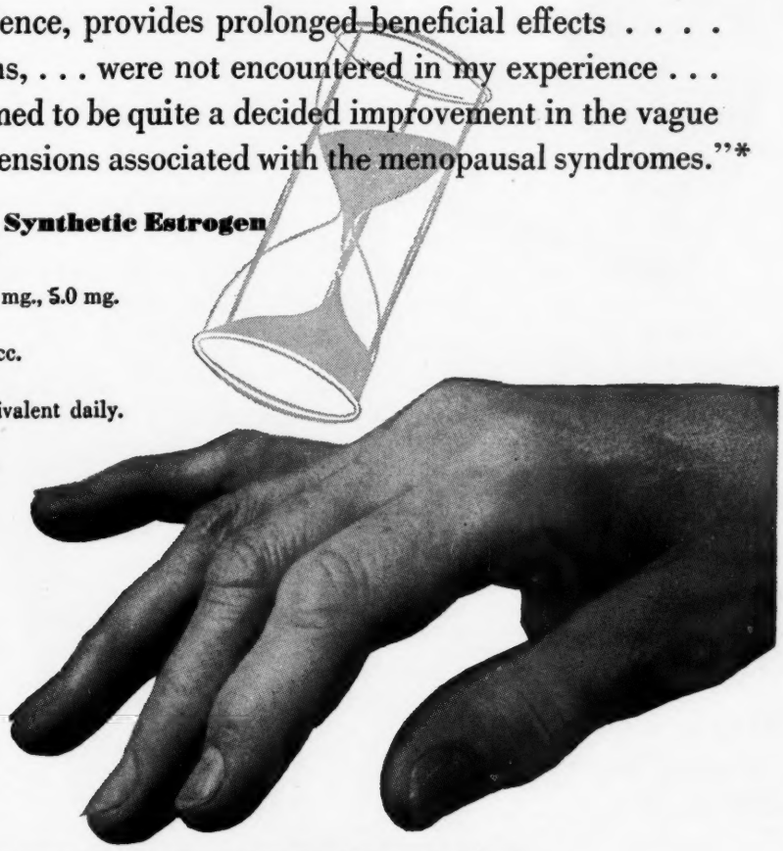
Average Dose: 1 to 2 mg. or equivalent daily.

*Hufford, A.R.: J.A.M.A., *123*, 269, (1943)



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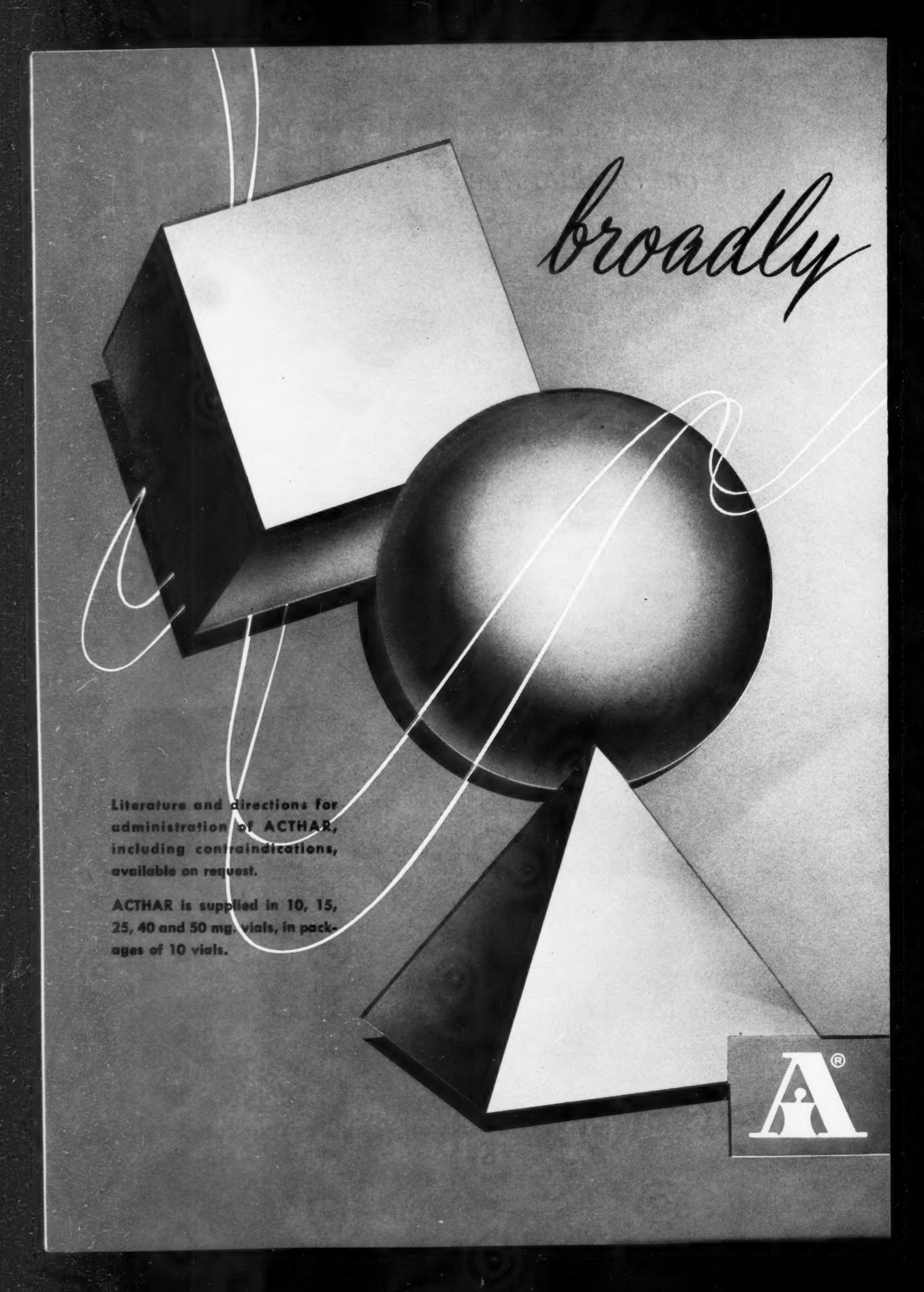
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After the optimal dose has been determined for the patient, the prescribing of the largest possible tablet size will result in the greatest saving. Literature describing the action, uses, and administration of Veriloid is available on request.

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FAT	10.5 Gm.	COPPER	0.2 mg.	VITAMIN C	10 mg.
CARBOHYDRATE	22 Gm.	VITAMIN A	1000 I.U.	VITAMIN D	140 I.U.
CALCIUM	370 mg.	VITAMIN B_1	0.39 mg.	CALORIES	225
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*Based on average reported values for milk.

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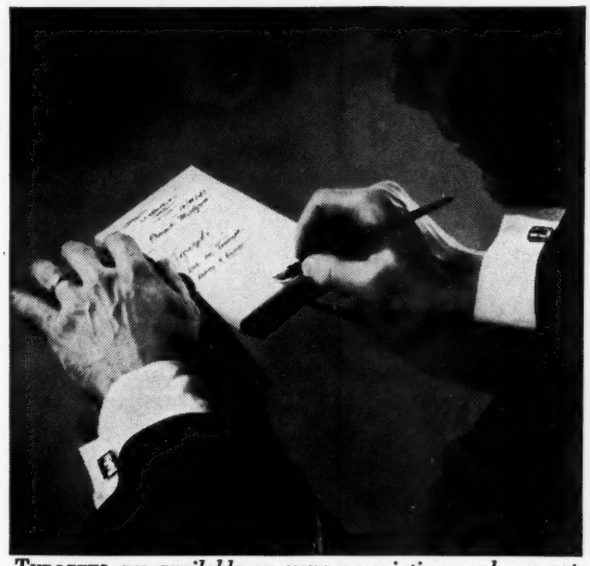
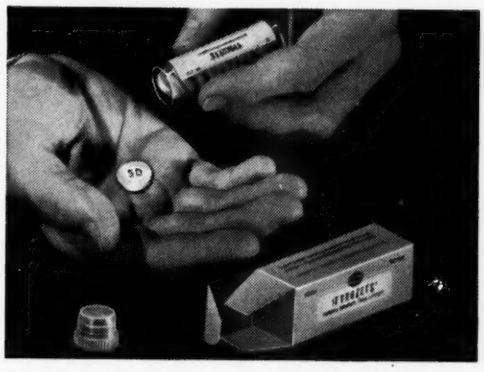


TYROZETS *are available on your prescription, and are not advertised to the public.*



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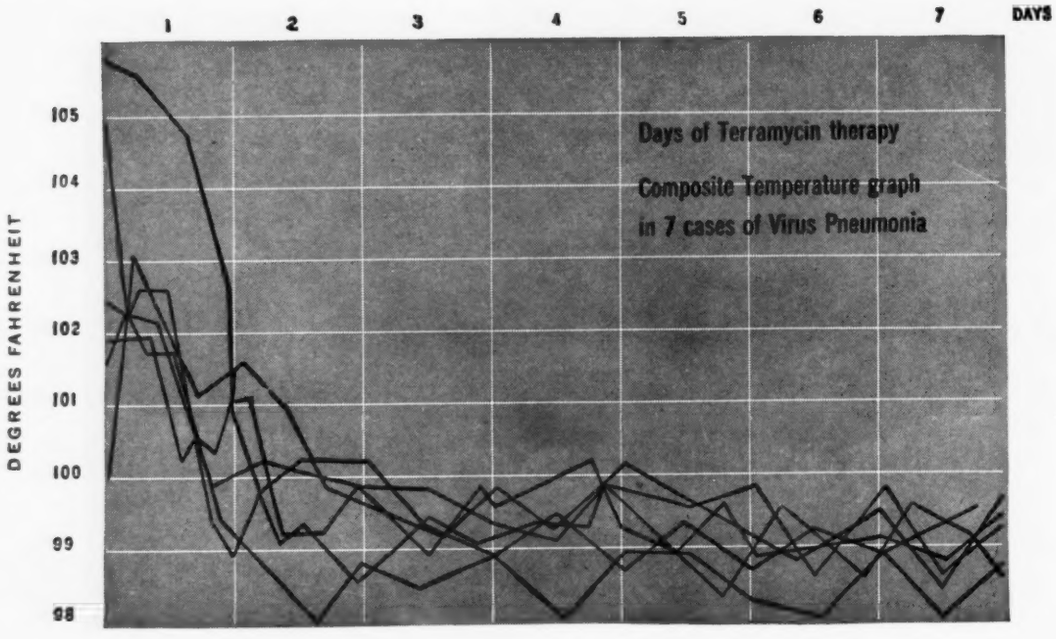
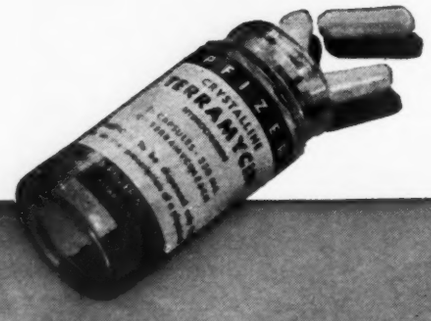
PRIMARY ATYPICAL VIRUS PNEUMONIA



CRYSTALLINE

Terra

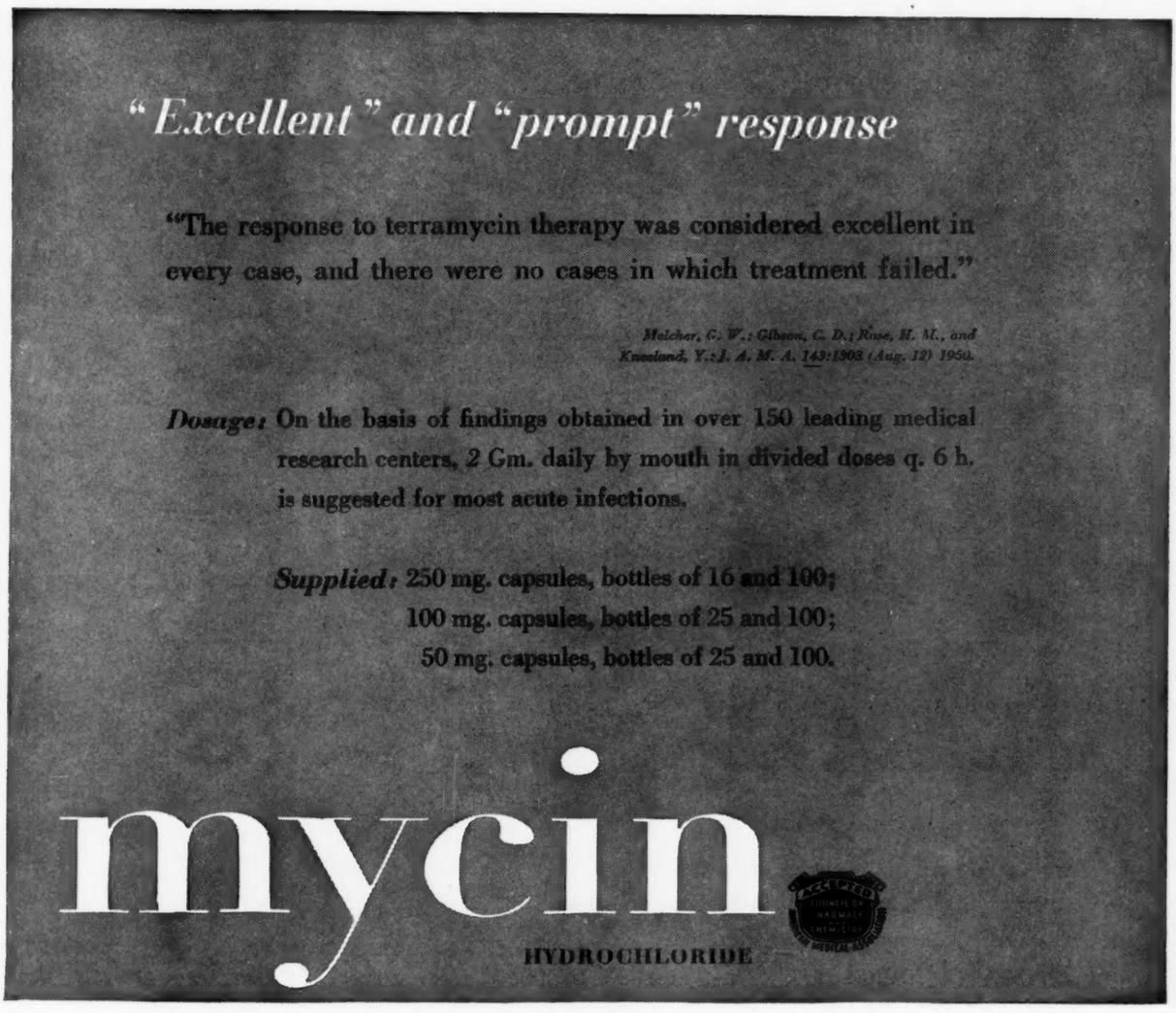


"Prompt fall in temperature occurred in every patient within thirty-six hours after the first dose of terramycin, and in no case was there a febrile relapse."

"Demonstrable clinical improvement was usually evident within a few hours after institution of therapy."

Meidner, C. W.; Gibson, C. D.; Rose, H. M., and Kuceland, Y.: J. A. M. A. 143:1303 (Aug. 12) 1950

Antibiotic Division **Pfizer**



Terramycin may be highly effective even when other antibiotics fail.[1]

Terramycin may be well tolerated even when other antibiotics are not.[2]

1. *Blake, F. G.; Friou, G. J., and Wagner, R. R.; Yale J. Biol. and Med. 22:495 (July) 1950.*
2. *Herrell, W. E.; Heilman, F. R.; Wellman, W. E., and Bartholomew, L. A.: Proc. Staff Meet. Mayo Clin. 25:183 (Apr. 12) 1950.*

CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*

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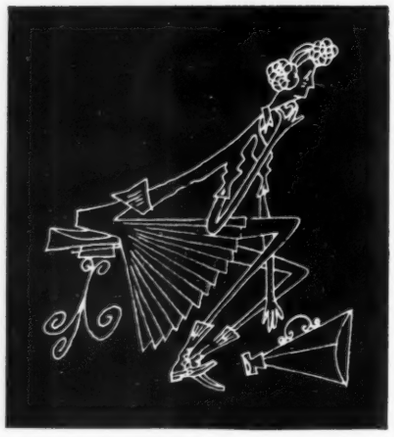

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1. Acnomel's cosmetic effectiveness hides the lesions. Your patient looks her best by day or night.
2. Acnomel's therapeutic effectiveness brings rapid improvement.

In the Journal of the A.M.A. (142:715), Dexter reports on Acnomel's cosmetic and therapeutic effectiveness:

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"Acne was either arrested or decidedly improved in all cases."

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protection
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action
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aminophylline
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and
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capillary
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presents
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hazard
—bottles
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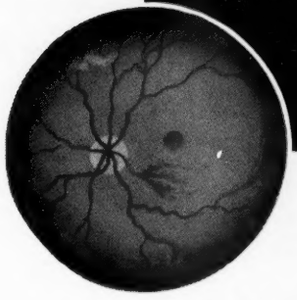
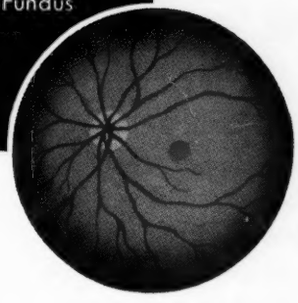
100
tablets

Ocular Fundus in Degenerative Vascular Disease—Hypertension, Diabetes, Arteriosclerosis—note tortuous blood vessels, areas of exudation, hemorrhagic areas.



Normal Ocular Fundus



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Combining Benadryl® hydrochloride, pioneer antihistaminic, with established non-narcotic remedial agents, **BENYLIN EXPECTORANT** relieves cough – whether due to allergy or the common cold. It's the Benadryl (10 mg. per teaspoonful) in this pleasingly-flavored syrupy vehicle which accounts for the highly effective decongestant and antispasmodic action of **BENYLIN EXPECTORANT.** And – because of its Benadryl content – **BENYLIN EXPECTORANT** also helps to relieve other distressing cold symptoms.

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Dosage: One to two teaspoonfuls every two to three hours. Children, one-half to one teaspoonful every three hours.

BENYLIN EXPECTORANT contains in each fluidounce:

Benadryl hydrochloride (diphenhydramine hydrochloride, Parke-Davis)	80 mg.
Ammonium chloride	12 gr.
Sodium chloride	5 gr.
Chloroform	2 gr.
Menthol	1/10 gr.

BENYLIN EXPECTORANT is supplied in 16 oz. and gallon bottles.

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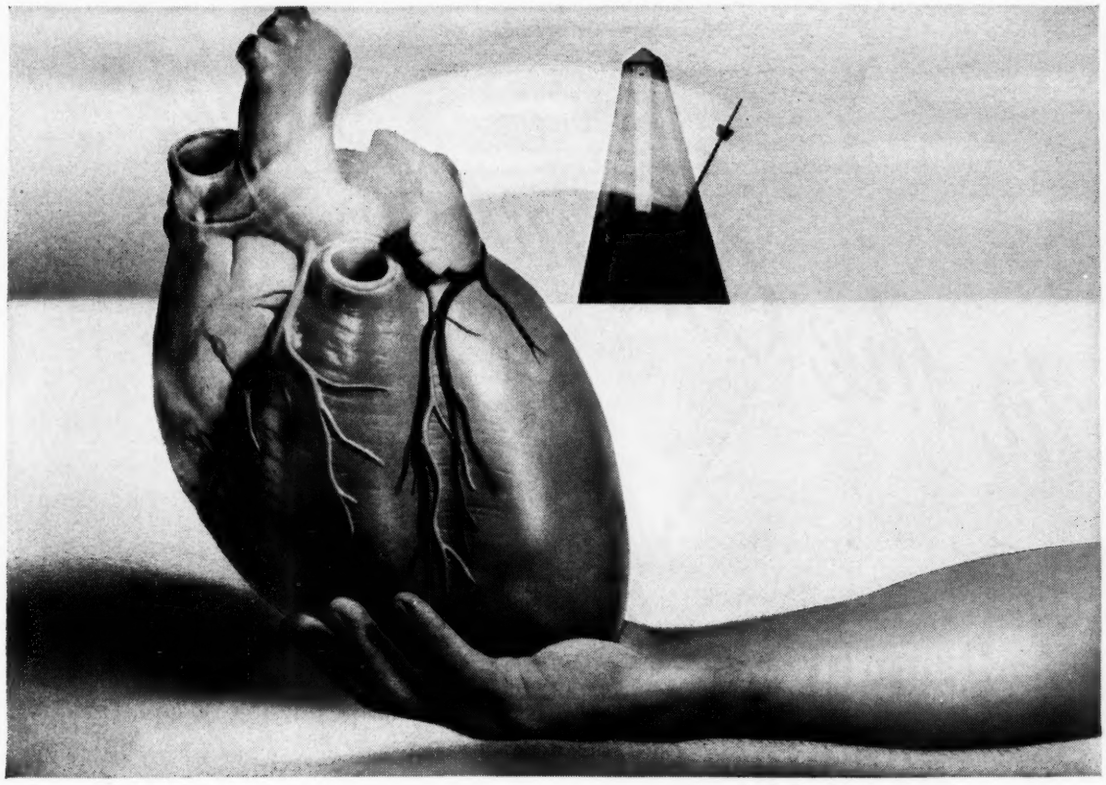

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Chief active principle* of digitalis purpurea (digitoxin)
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Troublesome rhinorrhea is mitigated by the action of atropine, while the typical muscular aches and pains respond to Dover powder, acetophenetidin, and aspirin. This multiple approach quickly makes for subjective comfort, minimizing the demands of the patient's vitality.

The dose of Dasin is 1 or 2 capsules every 2 hours for 3 doses, then 1 capsule every 3 hours. Supplied in bottles of 100 and 1000.

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Each Dasin capsule contains:

Dover powder	½ gr.
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Atropine Sulfate	1/500 gr.
Aspirin	2 gr.
Camphor	¼ gr.
Caffeine	⅛ gr.

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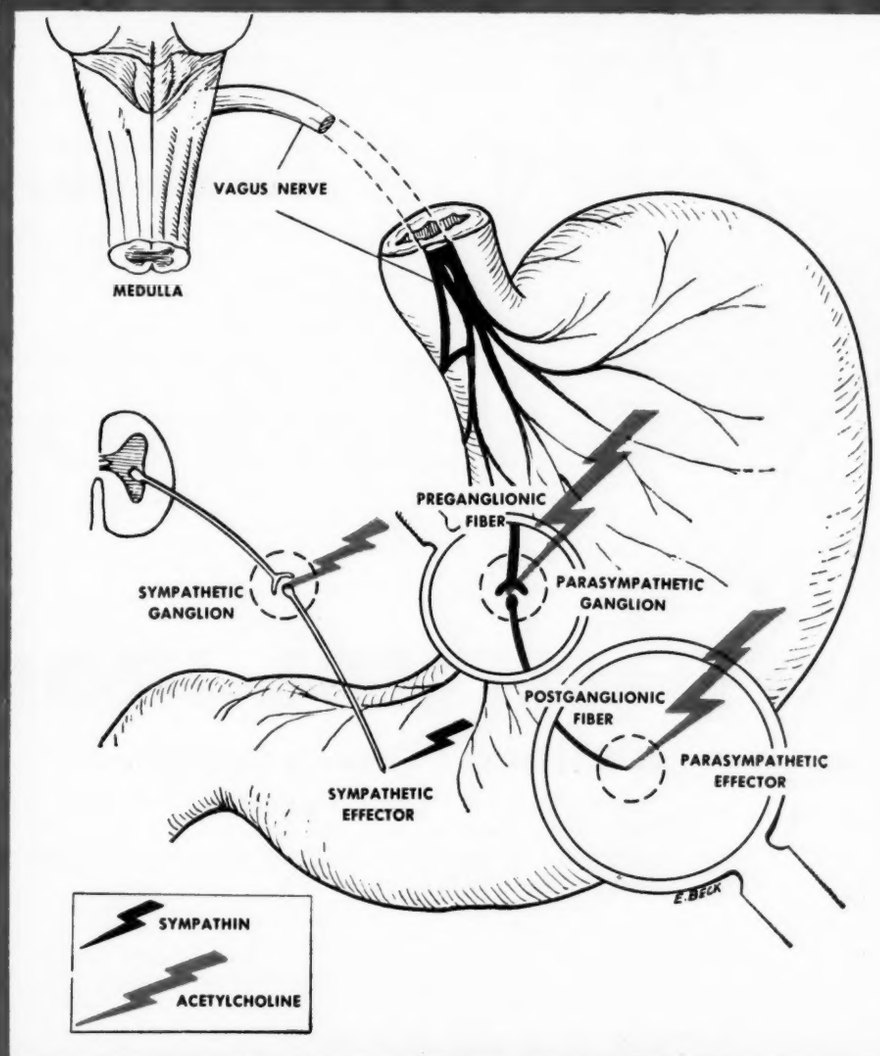
DASIN
CAPSULES



Banthine* Brand of Methantheline Bromide

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—a true anticholinergic drug, opposes the action of acetylcholine at the ganglions of the parasympathetic and sympathetic systems and at the nerve endings of the parasympathetic system.

Thus, it consistently decreases the hypermotility and in most cases the hyperacidity characteristic of ulcer diathesis.

Experience indicates that patients may be best served by prescribing two tablets of Banthine (100 mg.) every six hours day and night although a few patients may be satisfactorily treated with one tablet (50 mg.) on the same schedule.

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Molybdenized iron (White's Mol-Iron)—the most effective iron therapy known [1, 2, 3]—combined with ALL the known as well as the unidentified nutrients of desiccated WHOLE liver, plus supplemental vitamin factors, including vitamin B_{12}.

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Desiccated Whole Liver		0.45 Gm. (equivalent to 1.8 Gm. whole liver—minus water content only—not a fraction or an extract)
Thiamine hydrochloride		1 mg.
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Recommended dosage: 1 to 2 capsules three times daily after meals.
Supplied in bottles of 100 and 1000 capsules.

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Mol-Iron Tablets, small, easily swallowed.
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1. Dieckmann, W. J., and Priddle, H. D.: Am. J. Obstet. & Gynec. *57*:541 (1949).
2. Chesley, R. R., and Annitto, J. E.: Bull. Margaret Hague Mat. Hosp. *1*:68 (1948).
3. Healy, J. C.: The Jnl. Lancet *66*:218 (July) 1946.

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(brand of chlorprophenpyridamine maleate)

unusual potency
effective in dosages of 2 to 4 mg.

rapid onset of action
within 10 to 30 minutes

high tolerance
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prolonged relief
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Available forms: TABLETS, REPEAT ACTION TABLETS AND SYRUP.

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The American Journal of Medicine

VOL. X FEBRUARY, 1951 NO. 2

Editorial

Experience Should Be a Good Teacher

BECAUSE of the conflict in Korea this country is faced once more with the problem of supplying adequate medical care to the armed forces as well as to the civilian population—a problem far more difficult and complicated by the advent of atomic weapons and the threat of biologic warfare. The challenge is the greatest that our government has been called upon to meet and requires the wisest and most carefully devised plans to meet the immediate requirements of sufficient highly trained physicians to care for the armed forces; to insure a steady and increasing flow of skilled physicians, competent to deal with these vast new problems which threaten the public health; to maintain and build up our basic scientific researches, the results of which might well determine the outcome of a war; and finally, to carry on unimpaired and indeed improved medical care of our civilian population which provides our only pool of manpower should there be a world struggle for survival.

Clearly, the magnitude of this challenge demands a long range, farsighted program in which errors of the past are eliminated, in which the faculties of medical schools are not weakened but are brought to the highest efficiency, and in which the skills and abilities of physicians and medical scientists are utilized to the fullest.

In the first world war many of the faculties of medical schools were seriously depleted, interneships were shortened and postgraduate residencies almost abolished. Despite the recognition of these errors the same mistakes were repeated in the second world war but to an infinitely greater degree. Medical school faculties were needlessly depleted; basic medical research was drastically curtailed; medical scientists were called into positions in the armed services which were frequently wholly unrelated to their training so that their abilities and skills were wasted; interneships were needlessly shortened to nine months now generally agreed to have been a grave mistake; and residencies were reduced in number and in time. All of this resulted in sending to the armed services medical men with inferior training, and yet these men were immediately faced with difficult problems calling for the highest type of training. It also brought to a standstill in many laboratories the training of young medical men in the discipline of research. The over-all effect was a critical lowering of medical standards and a shortage of well trained men which is still felt today.

The number of physicians called into the military services was so far beyond the needs of the services that many had periods of idleness while the civilian population was, in some places, left with inadequate medical care. This fact was admitted in a public statement by the Secretary of War after the end of the war.

Since the Korean campaign started, there has been acute need for physicians in the services and everyone wants to see this need completely and efficiently met. Certain ominous signs, however, are beginning to

appear—talk of shortening interneships to one year, of shortening and decreasing the number of residencies, of acceleration of the medical curriculum, of drafting young scientists as fighting men and of cutting down on basic research. Some physicians are being called without regard to their essential need in civilian hospitals and medical schools; in short, a repetition of the costly errors of the last two wars.

No one is able to say at the present writing that we shall not be involved in a "cold war" or "armed peace" for fifteen or twenty years. If this is even a remote possibility, it is imperative that our medical schools be kept at the highest efficiency; that a steady and increasing flow of well trained physicians be produced by the schools; that these graduates have the best type of interneships available such as a minimum of two years for internal medicine and surgery; that a certain number of men be allowed to pursue or even to be assigned to advanced postgraduate training in the residencies in order to assure a supply of excellently trained internists, surgeons and specialists; that medical scientists be assigned to medical schools and kept there except for specific and special needs of their skills in the armed services, and if called for such special needs that they be returned to their schools after fulfilling those needs. If any part of this program should be drastically curtained for fifteen or twenty years—for the duration of a long "cold war"—a most crippling blow would be dealt to all research in medicine and the medical care for the military and civilian populations would deteriorate rapidly.

Never has there been a time when our country needs a pool of trained investigators more acutely than now. No one can predict all of the new problems that will confront the physician if atomic and biologic weapons are used on military and civilians alike. It is absolutely essential, therefore, that the medical schools and their allied hospitals, as well as the other qualified hospitals, continue or even increase the training of young medical scientists who can meet new problems and emergencies in the health field; nor was there ever a time when physicians were called upon to meet such complex health hazards as would be the case in a war today. It follows that the medical schools and hospitals should bend all efforts to improve the quality of the physicians who leave their doors to take care of the civilian and military populations, and to resist all steps that would decrease the efficiency and quality of the graduates. The actual number of physicians and medical scientists essential for maintenance of the efficiency of our medical schools and teaching hospitals is relatively small; yet these men will insure a steady flow of highly trained physicians for the military services if they are not disturbed except for special use of their skills.

It is equally important that a steady flow of good students into the medical schools be maintained, and plans for insuring this are said to be under way.

It is absurd to argue that basic research be dropped and be replaced with research having to do with the war effort. Nothing could play more into the hands of the enemy than to disrupt basic research in this country. In the last war application of the fruits of basic research to war problems was a determining factor in the final victory. In the war which threatens us now we shall be greatly outnumbered and it is only too clear that we shall have to depend increasingly upon our scientists and their knowledge and skills. The country armed with the best group of scientists in any future war stands the best chance of surviving.

In planning for such an indefinite period of "cold war" or for an eventual all-out war all our thought and effort should be bent toward increasing the efficiency of our medical faculties in teaching and in their scientific contributions, medical curricula, interneships, residencies and graduate training. Acceleration of curricula, drafting of essential faculty members and medical scientists, shortening of interneships, residencies and postgraduate training can lead

to but one end—a dangerous undermining of the essential medical and scientific contributions and services which are vital to survival.

It is urgently hoped and expected that the governmental agencies responsible for allotment of physicians and the Department of Defense will act immediately not only to avoid the mistakes of the last war but also to set up a wise long-range plan which will insure an alert body of medical scientists and the best possible care for the military and civilian populations.

JOSEPH T. WEARN, M.D.

Clinical Studies

Effect of Adrenocorticotropic Hormone (ACTH) on Beryllium Granulomatosis and Silicosis*

B. J. KENNEDY, M.D.,† J. A. P. PARE, M.D., K. K. PUMP, M.D., J. C. BECK, M.D., L. G. JOHNSON, M.D., N. B. EPSTEIN, M.D., E. H. VENNING, PH.D. *and* J. S. L. BROWNE, M.D.

Montreal, Canada

INVESTIGATION of the effects of adrenocorticotropic hormone (ACTH) and cortisone has demonstrated alterations in cellular and fibrous tissue reactions.[1,2] Other studies have recorded a lowering of the concentrations of serum globulin and the return to normal of albumin-globulin ratios.[3] Since chronic beryllium granulomatosis (delayed chemical pneumonitis) is characterized by fibrous tissue and cellular reactions and by hyperglobulinemia,[4] an alteration of this disease might therefore be expected to occur on administration of ACTH or cortisone.

Beryllium granulomatosis is a progressive pulmonary disease characterized by fatigue, exertional dyspnea, cough and weight loss.[4,5,7] X-rays demonstrate diffuse pulmonary changes.[5,6] Microscopically the lesions consist of multiple granulomas, increased fibrosis in the interalveolar septa and in the granulomas, and dense collagen deposits. A cellular reaction, predominantly of lymphocytes and mononuclear cells, may be found in the interalveolar walls, between focal lesions and at the periphery of the nodular granulomas.[8,9]

It seemed reasonable to expect that if the lesions of beryllium granulomatosis resolved or the cellular infiltration diminished, the impairment of pulmonary circulation and air exchange would decrease and more normal respiratory function might occur.

Adrenocorticotropic hormone (ACTH) was administered to two patients with chronic beryllium granulomatosis. A striking improvement in both occurred as evidenced by the clinical response and improvement in x-rays and respiratory function studies.[10] A third patient, similarly treated by Thorn et al.,[11] improved.

During the course of this study, the possibility of ACTH altering other chronic pulmonary diseases characterized by fibrosis or cellular reactions was also considered. Silicosis was one of these. One patient was treated. Silicotic nodular lesions consist pathologically of epitheliod cells, proliferating fibroblasts and collagen surrounding spicules of silica. Occasionally a cellular infiltration is present.[12] The lesions of silicosis tend to be discrete in contrast to the diffuse, interalveolar cellular infiltration demonstrated in beryllium granulomatosis.

A detailed report of the metabolic and respiratory studies of three patients, two with beryllium granulomatosis and one with silicosis, follows:

* From the McGill University Clinic, Royal Victoria Hospital, Montreal, Canada. This research was supported in part by a Damon Runyon Clinical Research Fellowship to one of us (B. J. K.), recommended by the Committee on Growth of the National Research Council, and administered by the American Cancer Society, Inc., New York City; by a grant from the National Research Council, Ottawa, to Dr. J. S. L. Browne; and by the Sylvania Electric Products, Inc., Salem, Massachusetts.

† Now at The New York Hospital, New York City.

METHOD OF STUDY

The patients were studied on a metabolic ward and were given a constant measured diet. Complete twenty-four-hour urine collections were obtained, the accuracy of which was checked by creatinine determinations. Nitrogen balance studies were conducted, employing a factor of 1.3 gm. per twenty-four hours for the fecal nitrogen.[13] Electrolyte studies consisted of serum and urinary electrolyte determinations.

The following methods were employed: Sedimentation rate by the Westergren method, sodium by the method of Butler and Tuthill,[14] chloride (Wilson and Ball[15]), potassium (Breh and Goebler method as modified by Neufeld[16]), serum uric acid (modification of Folin method[17]), urine uric acid (uricase method of Schaffer[18]), vitamin C (Roe and Kuether[19]), glutathione (modification of Fujita[20]), cholesterol (Liebermann-Burchard reaction[21]), cholesterol ester (modification of Bloor and Knudson[22]), serum total protein (Peters and Van Slyke[23]), serum albumin (Howe[26]), non-protein nitrogen (Folin and Wu[27]), urine creatinine (modification of Folin and Wu[25]), urine nitrogen (Peters and Van Slyke[24]), carbon dioxide combining power (Van Slyke and Cullen[28]), thymol turbidity (modification of Shank and Hoagland[29]) and calcium (modification of Kramer and Tisdall[30]).

The urinary 17-ketosteroids were measured by the method of Callow, Callow and Emmens[31] and a correction factor eliminating chromogens was applied.

The glucocorticoids were determined by the bioassay method of Venning, Kazmin and Bell, which is dependent upon the glycogen deposited in the livers of fasted adrenalectomized mice. The values are expressed in terms of micrograms of the standard, 11-dehydro-17 hydroxy corticosterone (cortisone).[32] The adrenal cortical metabolites were also determined by a modification of the chemical method of Daughaday, Jaffe and Williams,[33] the analysis being conducted on the water soluble fraction.

The beryllium in the urine was measured chemically.* The amounts excreted by patients with beryllium granulomatosis during twenty-four hours vary between 0 and 0.4 micrograms, the lower limit of sensitivity of the method being about 0.05 micrograms of beryllium in twenty-four hours.[34]

* We are indebted to Dr. Friedrich Klemperer of the Trudeau Foundation Laboratories, Saranac Lake, N. Y., for the chemical determinations of beryllium in the urine.

Respiratory function studies consisted of frequent vital capacity and maximum breathing capacity determinations. Residual air studies were carried out by a modification of an oxygen dilution method.[35] The index of alveolar mixing or nitrogen concentration in the alveolar air after a seven-minute period of breathing pure oxygen was determined at the same time. The initial findings in each patient were in accord with those previously reported in patients with beryllium granulomatosis.[36] Measurement of ventilation efficiency with the patient breathing room air and with the expired air being collected in Douglas bags was done at rest and with standard weight-lifting exercise several times during the study. In patients L. H. and J. M. the work performed was 3,200 foot pounds in four minutes, and in B. W. only 1,600 foot pounds.

Psychiatric interviews were limited to observations of the patients' reactions during treatment. No formal psychotherapy was attempted. Psychologic testing was conducted separately by a clinical psychologist in the Allan Memorial Institute.

Adrenocorticotropic hormone (ACTH)* was administered intramuscularly in equally divided doses every six hours. Cortisone† was injected intramuscularly at twenty-four-hour intervals.

CASE REPORTS

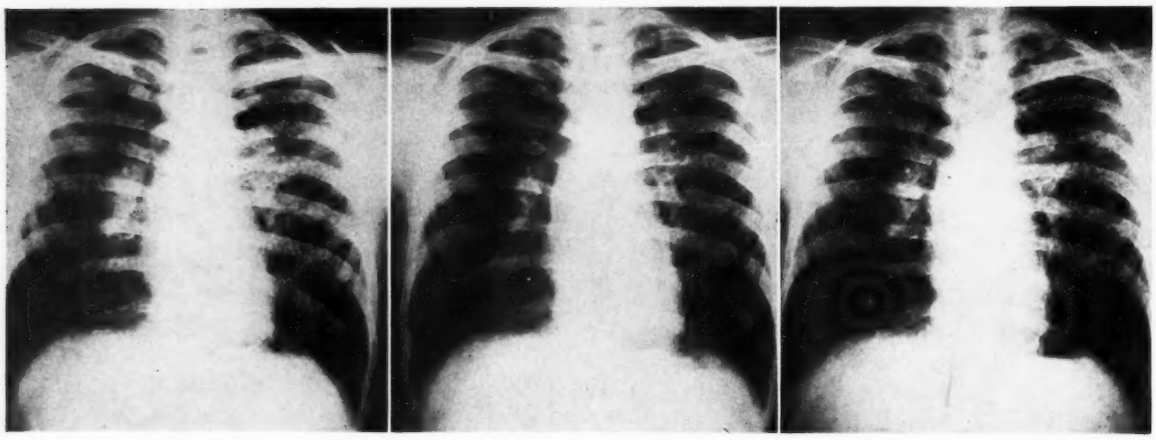
The following are clinical case reports of the patients studied. Pertinent laboratory findings are recorded on charts which are referred to in the discussion in order to simplify the case histories.

BERYLLIUM GRANULOMATOSIS

CASE 1. L. H., a male, age twenty-seven (Figs. 1 to 8), was employed in a fluorescent lamp manufacturing plant from September, 1940, to April, 1943, where exposure to beryllium dust occurred. In July, 1947, cough, dyspnea on exertion, weight loss of 10 pounds and weakness were noted. A chest x-ray revealed a diffuse granulomatous process in both lungs and hilar node enlargement. During the subsequent two years, the disease gradually progressed as evidenced by marked dyspnea even on mild exertion, and an increase in the extent of the pulmonary lesions.

* The ACTH was generously supplied by Dr. John R. Mote of the Armour Laboratories, Chicago.

† Cortisone is a product of Merck & Company, Inc.



1A 1B 1C

FIG. 1. A, L. H. (Case 1), appearance of the lungs prior to ACTH administration. B, decrease in density of pulmonary nodules and decrease in size of hilar nodes after the third week of ACTH. C, two months after ACTH therapy the nodules are more dense, but improvement is still evident.

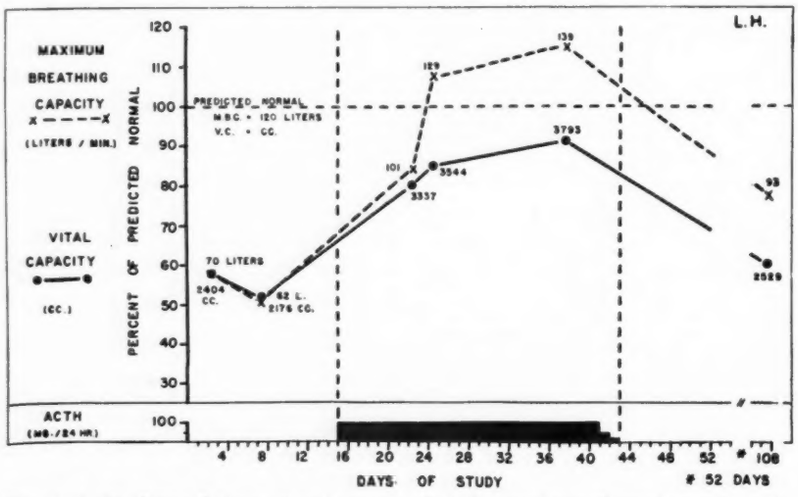


FIG. 2. L. H. (Case 1) showed an increase of vital capacity and maximum breathing capacity during ACTH therapy.

The patient was admitted to the McGill University Clinic, Royal Victoria Hospital, on January 21, 1950, for study. Fatigue, weakness, dyspnea and mild non-productive cough continued to be the chief complaints. Examination revealed an asthenic man weighing 128 pounds. The temperature was normal. The respiratory rate was increased at rest, usually being 28 per minute, and was further increased by only moderate exercise. The pulse varied between 70 and 80 per minute. There was intercostal retraction on inspiration. Many fine, moist, crackling rales were present throughout the entire chest. The pulmonic second sound was accentuated, the heart size was normal and numerous extrasystoles were present. Moderate clubbing of the fingers was noted.

X-rays of the chest revealed accentuated pulmonary markings, a diffuse infiltration of small nodular densities throughout both lung fields and enlarged hilar nodes. (Fig. 1A).

On February 7, 1950, following a fifteen-day control period, adrenocorticotropic hormone (ACTH), 100 mg. daily, was administered and continued for twenty-eight days.

During the four weeks of therapy a striking improvement occurred. The pulmonary rales gradually disappeared during the first week of ACTH injection and the lungs remained clear to auscultation thereafter. These changes were accompanied by a decrease in dyspnea on exertion. During the third week the resting respiratory rate decreased and the pulmonic second sound became less accentuated. Climbing

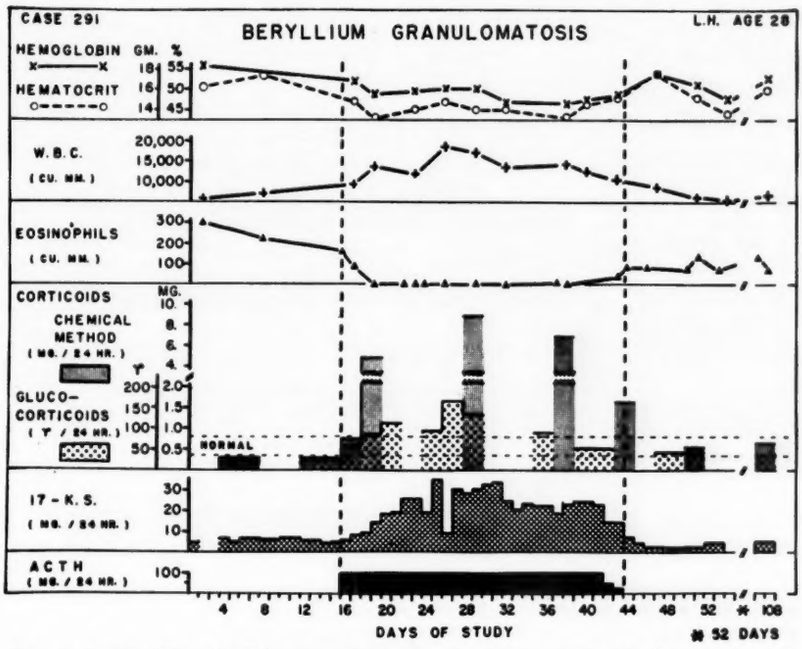


FIG. 3. L. H. (Case 1) showed an increase of urinary corticoids (bio-assay and chemical methods) and 17-ketosteroids, and decrease in eosinophils during ACTH administration.

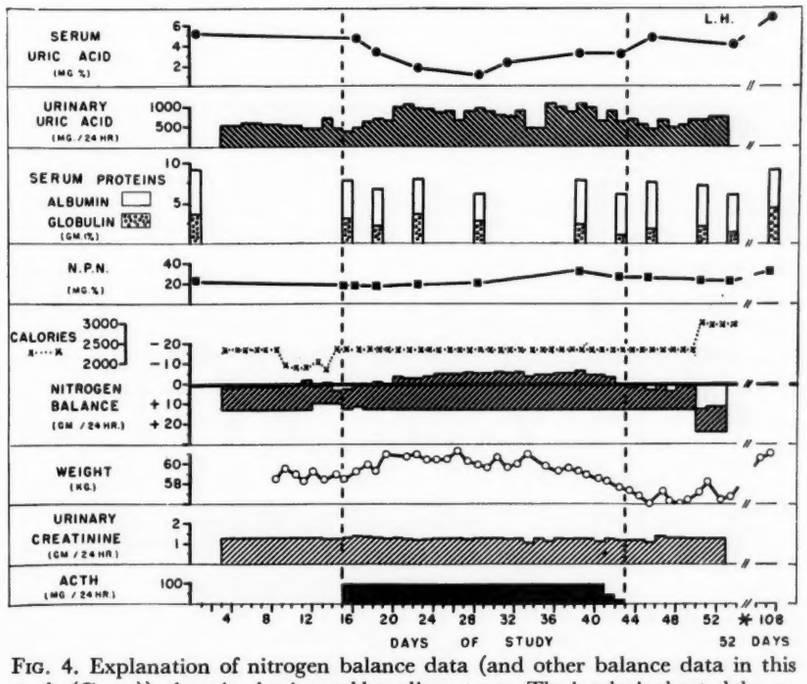


FIG. 4. Explanation of nitrogen balance data (and other balance data in this study (Case 1)); there is a horizontal base line at zero. The intake is charted downward from this base line; the urinary and fecal excretions are then measured upward from the intake line toward the base line. If the output exceeds the intake, the final level will be above the base line; if the output is less than the intake, the final level will be below the base line. Thus a negative balance is indicated by a shaded area above the base line and a positive balance by a clear area below the base line.

four flights of stairs produced no distress, though before ACTH was begun a few steps produced severe dyspnea. Toward the end of the fourth week of ACTH increased aggressiveness and emotional instability necessitated discontinuance of the hormone. There appeared to be no clinical impairment of respiratory function at that time.

X-rays demonstrated a gradual decrease in pulmonary markings, an apparent decrease in size and density of nodules, decrease in the size of hilar nodes and clearing of the lungs. (Fig. 1B.) However, the nodular densities had not entirely disappeared.

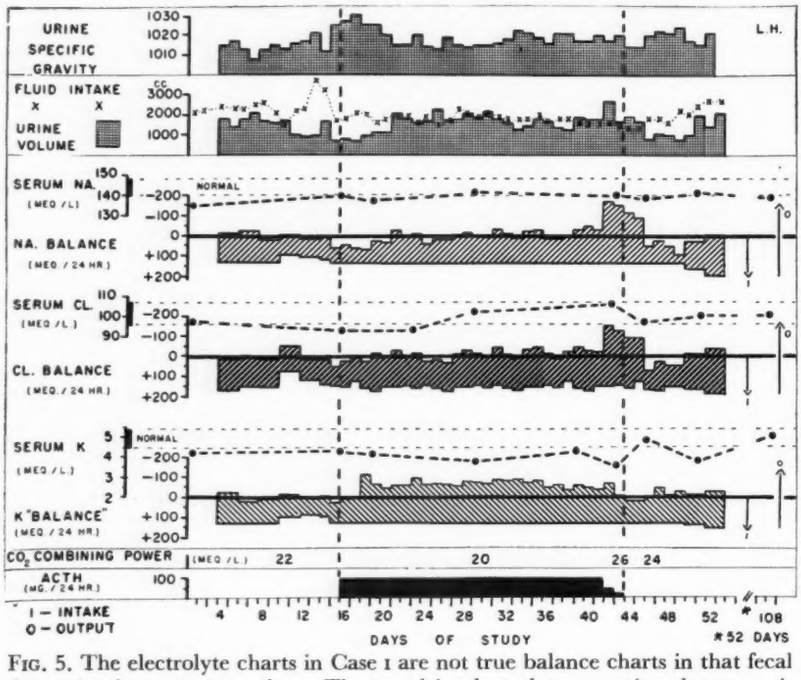


FIG. 5. The electrolyte charts in Case 1 are not true balance charts in that fecal determinations were not done. The trend in electrolyte excretion, however, is demonstrated.

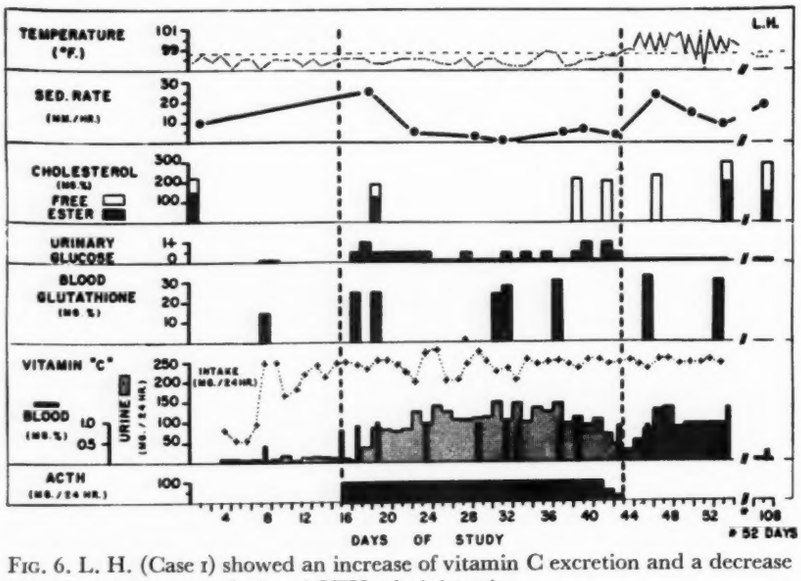


FIG. 6. L. H. (Case 1) showed an increase of vitamin C excretion and a decrease of sedimentation rate during ACTH administration.

On withdrawal of ACTH the patient developed weakness, fatigue and daily spiking

fever to 100.8°F. The fever persisted for two weeks and the weakness diminished a week later.

Two months after ACTH therapy the patient appeared well and had gained 5 pounds in weight. Weakness and dyspnea on exertion were

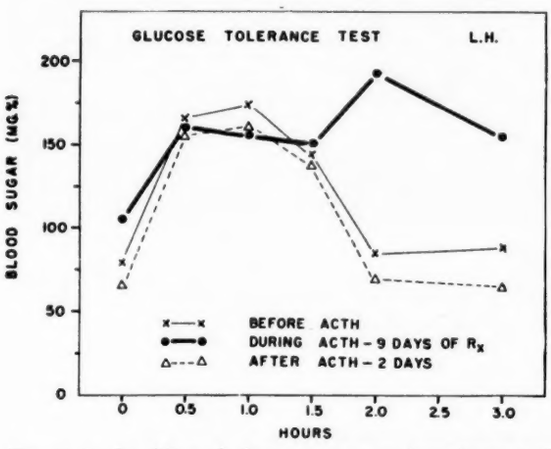


FIG. 7. L. H. (Case I) demonstrates an impairment of glucose tolerance during ACTH administration; hormone was administered twenty-eight days.

present but less marked than before therapy. Respirations were 22 per minute and the pulse rate was normal. Fine crepitant rales were present at both lung bases posteriorly and the pulmonic second sound was accentuated. Clinically, the patient appeared better than before therapy but not as well as at the completion of ACTH administration.

X-rays of the chest demonstrated some regression of the improvement, the nodular lesions being more prominent. (Fig. 1C.)

CASE II. B. W., male, age thirty-three, (Figs. 9 to 15), developed a dry cough, fatigue, anorexia and slight dyspnea on exertion, in December, 1946. A weight loss of 20 pounds occurred. A chest x-ray revealed changes consistent with chronic beryllium granulomatosis. The patient had been employed in a fluorescent lamp factory from 1941 to June, 1942, during which time exposure to beryllium dust occurred. In 1946 the patient was again employed by the same firm for nine months prior to the onset of symptoms of the pulmonary disease. During the ensuing three years cough and dyspnea increased and x-rays of the chest demonstrated progression of the disease.

The patient was admitted for study to the McGill University Clinic, Royal Victoria Hospital, on March 21, 1950. Chief complaints were fatigue, anorexia, inability to gain weight, productive cough and dyspnea on mild exertion. Examination revealed a small, asthenic man weighing 93 pounds. The respiratory rate was increased at rest, averaging 28 per minute. The pulse was 120 per minute; blood pressure

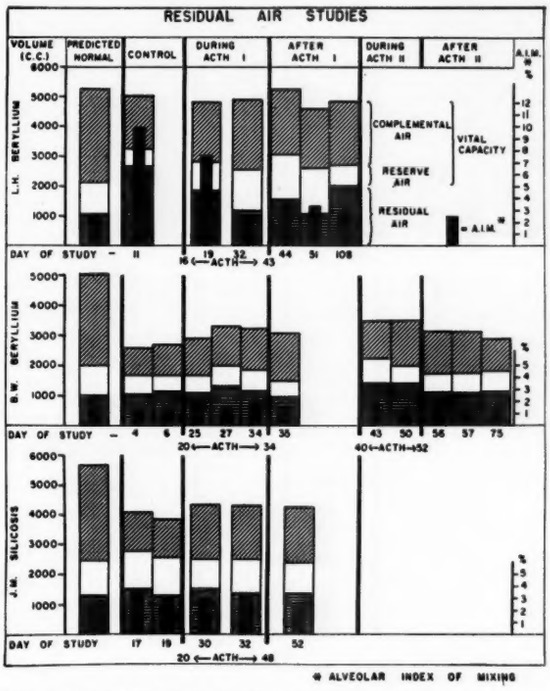
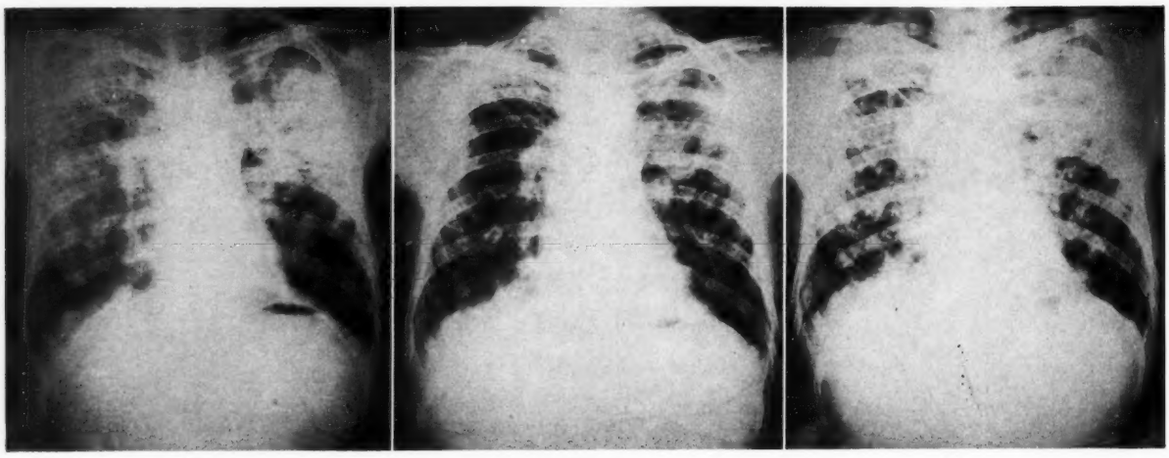


FIG. 8. Residual air determinations of three patients; the dose of ACTH was 100 mg. daily, except for an increase in the patient with silicosis to 160 mg. daily on the thirty-fifth day of study.

110/75. Respirations at rest were labored and the use of the accessory muscles of respiration was noted. Marked intercostal retraction, apical retraction and flaring of the costal margins occurred on inspiration. There was dullness to percussion over the apices anteriorly and posteriorly, particularly on the right. Marked bronchial breathing was heard over the right apex and scattered crepitant rales were present in the left axillary line. The pulmonic second sound was accentuated and the heart size was normal. Early clubbing of the fingers was observed.

Fluoroscopic examination demonstrated only slight movement of both diaphragms. Chest x-ray revealed conglomerates of diffuse nodular lesions in both upper lung fields and marked fibrosis. The lower lung fields showed scattered, punctate shadows. (Fig. 9A.) Skin tests for tuberculosis were negative, and venous pressure and circulation time recordings were normal.



9A 9B 9C

FIG. 9. A, B. W. (Case II), appearance of the chest x-ray before ACTH administration. B, clearing of lung fields and decrease in the size of nodules on the ninth day of the second course of ACTH (forty-eighth day of study). C, return of pulmonary densities twenty-five days after completion of the second course of ACTH.

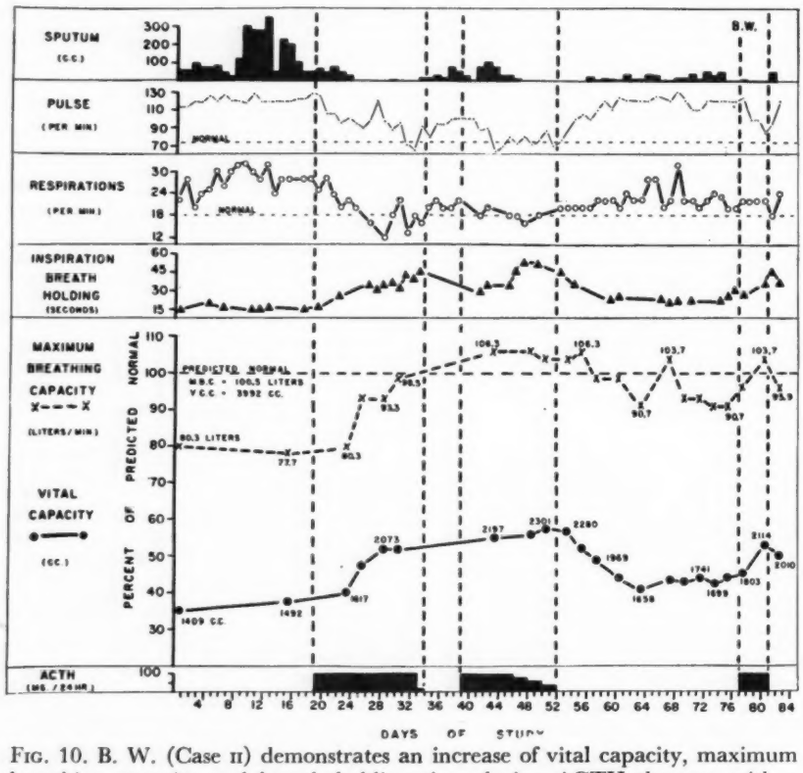


FIG. 10. B. W. (Case II) demonstrates an increase of vital capacity, maximum breathing capacity and breath holding time during ACTH therapy, with a corresponding decrease in sputum volume, pulse and respiratory rate.

Following a three-week control period administration of adrenocorticotropic hormone was begun April 12, 1950, at a dose of 100 mg. daily, and continued for fifteen days.

During the first week of ACTH therapy breathing became less labored, the cough decreased, appetite increased and there was a feeling of well being. Pulse and respirations decreased and the volume of sputum diminished. In the second week the patient was able to climb four flights of stairs although prior to therapy only a few steps could be ascended. Respirations were 12 per minute, pulse 66 per minute and the sputum had disappeared. The lungs were clear on auscultation. Toward the end of the second week of ACTH the patient's

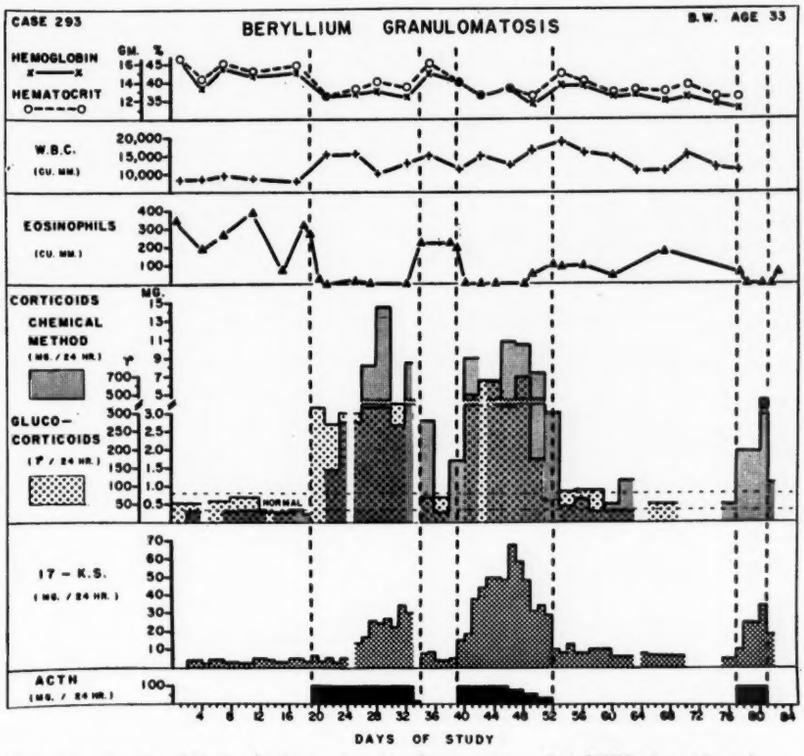


FIG. 11. B. W. (Case II) shows in the first course of ACTH that the glucocorticoids reached the maximum more promptly than the chemical corticoids although the latter rose to their maximum within twenty-four hours in the second course. An increase in 17-ketosteroids and fall in eosinophils occurred during the ACTH administration.

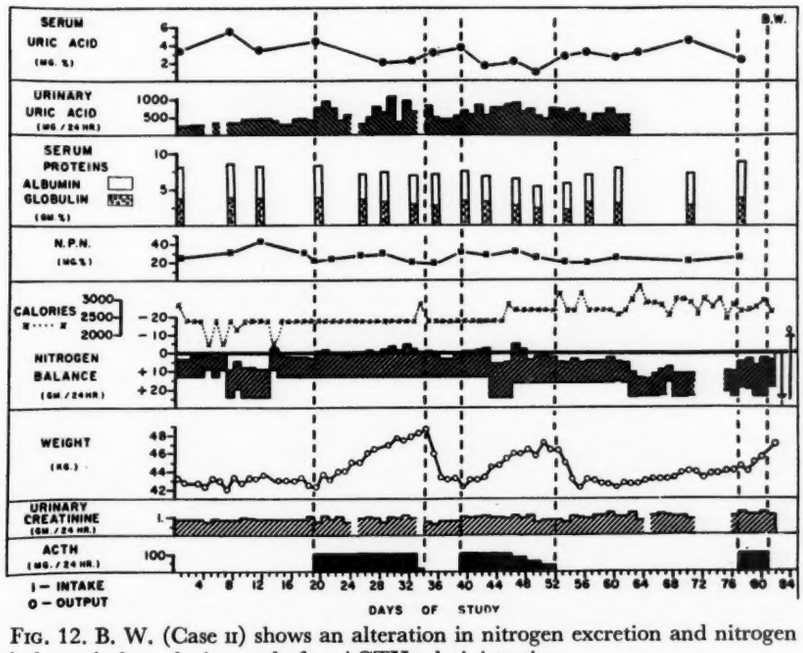


FIG. 12. B. W. (Case II) shows an alteration in nitrogen excretion and nitrogen balance before, during and after ACTH administration.

weight had increased 14 pounds, concomitant with the appearance of moderate ankle edema and massive edema of the genitalia. Thereupon ACTH was discontinued and a rapid diuresis followed.

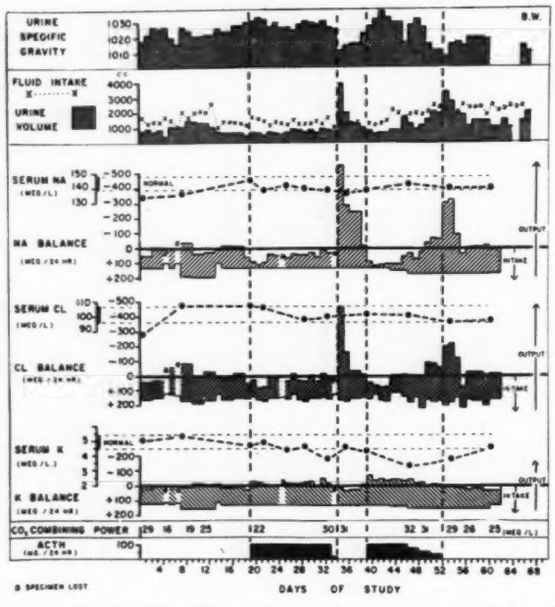


FIG. 13. B. W. (Case II) demonstrates retention of sodium, chloride and water during ACTH therapy. On cessation of the hormone an increased excretion of these constituents occurred.

After an interval of five days treatment with ACTH was recommenced at a dosage of 100 mg. daily. This was continued for seven days and slowly reduced in amount over another six-day period. The improvement persisted. Mild edema was again noted near the end of this second course of therapy.

X-ray of the chest near the completion of the second course of ACTH demonstrated a partial clearing of the lung fields, especially in the apices. The smaller nodules in the lower lung fields were decreased in size. (Fig. 9B.)

Following cessation of the second course of ACTH, the patient was observed for twenty-five days. Almost immediately a daily spiking fever occurred which persisted for two weeks. Weakness and fatigue again became prominent symptoms. Associated with this was a severe frontal headache. X-rays of the sinuses were normal. The pulse returned in seven days to the previous high level of 120 per minute, respirations increased to 22 per minute and the daily sputum volume increased slightly. No cough was present and the lungs remained clear to auscultation. A chest x-ray twenty-five days after the cessation of therapy revealed a partial return in the density of the lesions, especially in the upper lobe of both lungs. (Fig. 9C.)

Finally, a third course of ACTH was begun on the seventy-eighth day of study. A dose of 100 mg. daily for five days was administered to observe the effect of a short course of ACTH. During the five days of therapy the patient's feeling of well being again increased, the pulse and respirations decreased and the appetite improved. On cessation of therapy these features

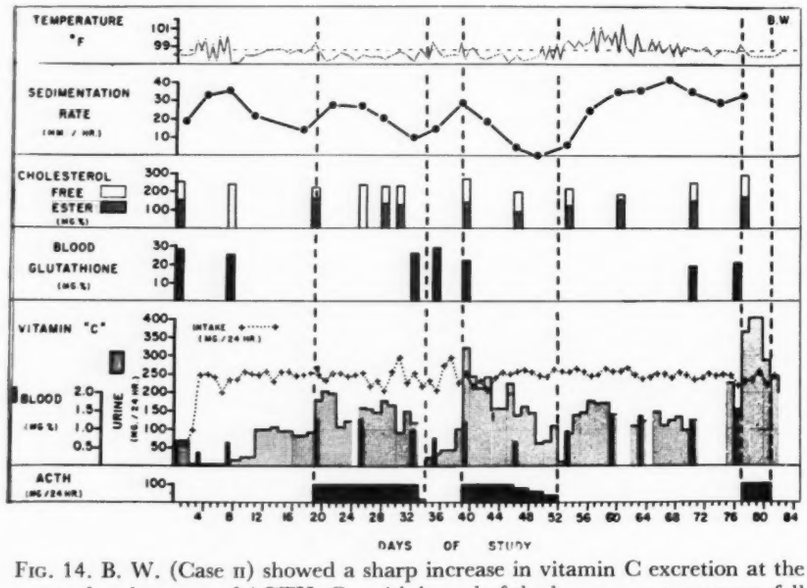


FIG. 14. B. W. (Case II) showed a sharp increase in vitamin C excretion at the onset of each course of ACTH. On withdrawal of the hormone a temporary fall below control levels was noted.

reversed to previous levels. The patient was discharged after eighty-three days of study. Six weeks later the patient continued to feel better than before the use of ACTH.

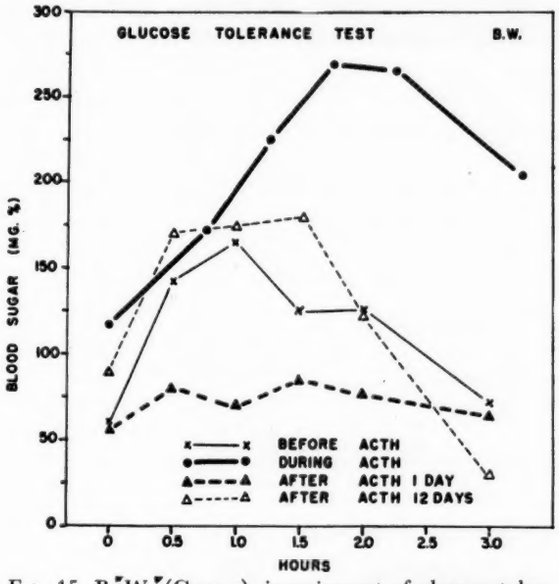


FIG. 15. B. W. (Case II), impairment of glucose tolerance during twenty-eight days of ACTH administration. One day following cessation of the hormone the glucose tolerance curve was flat.

SILICOSIS

CASE III. J. M., male, age thirty-seven, (Figs. 16 to 20), was first admitted to the Royal Victoria Hospital in September, 1949. Chief complaints were fatigue, productive cough and dyspnea on exertion for three years and weight loss of 20 pounds. The patient had worked in a silica mine from May, 1945, to September, 1946. A chest x-ray revealed numerous small dense nodular shadows throughout both lungs consistent with silicosis, grade three. The diagnosis was confirmed by a biopsy obtained at a right exploratory thoracotomy.

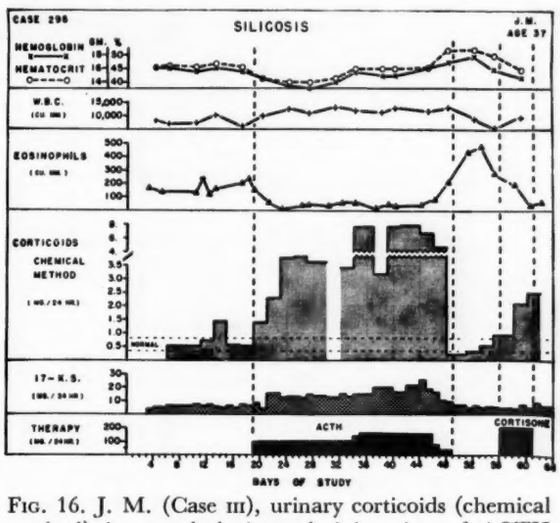


FIG. 16. J. M. (Case III), urinary corticoids (chemical method) increased during administration of ACTH and cortisone. An increase in 17-ketosteroids accompanied ACTH therapy only.

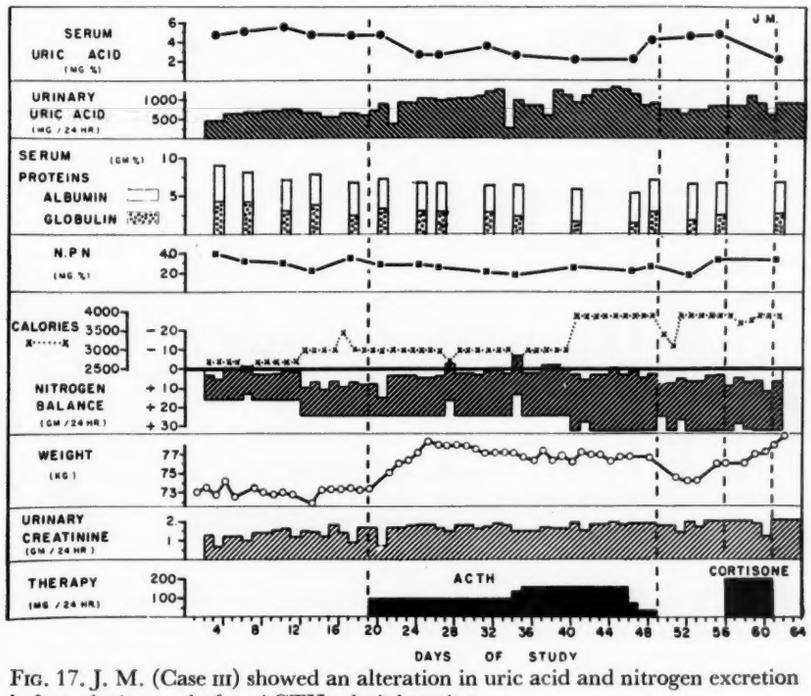


FIG. 17. J. M. (Case III) showed an alteration in uric acid and nitrogen excretion before, during and after ACTH administration.

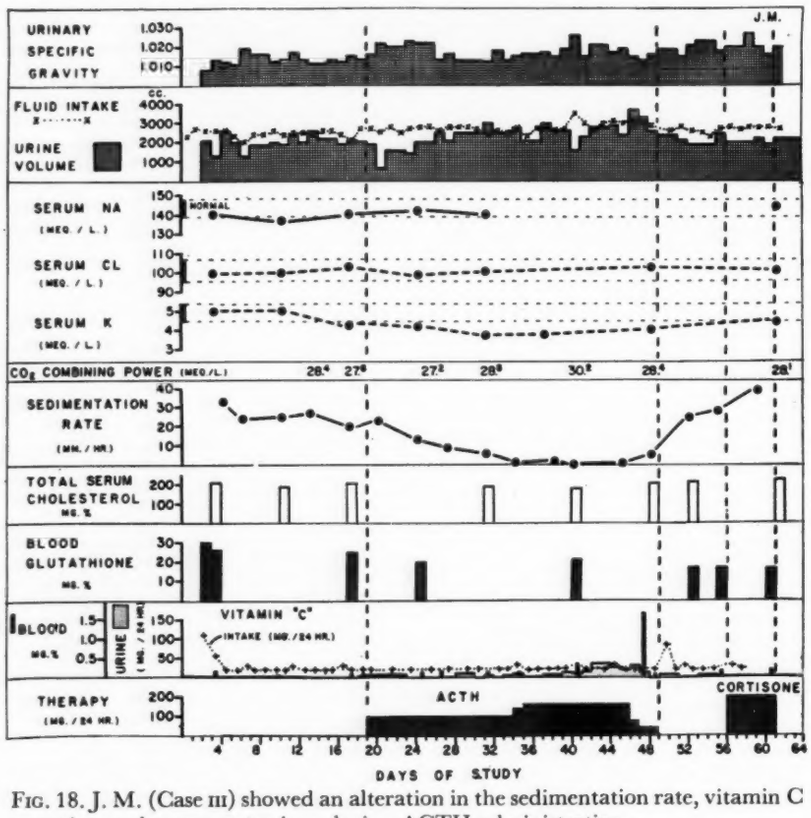


FIG. 18. J. M. (Case III) showed an alteration in the sedimentation rate, vitamin C excretion and serum potassium during ACTH administration.

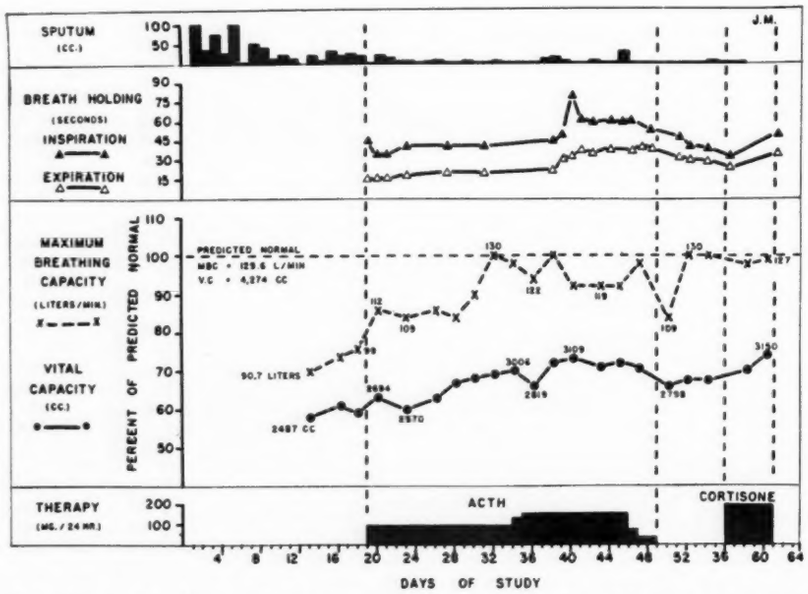


FIG. 19. J. M. (Case III), vital capacity, maximum breathing capacity and breath holding capacity improved during ACTH.

The patient was admitted to the McGill University Clinic, Royal Victoria Hospital, on April 28, 1950. Chief complaints were a mild productive cough and dyspnea on exertion. Examination revealed a well appearing man weighing 161 pounds. The pulse was 76 per minute and respirations 20 per minute. There were occasional crepitant rales throughout the chest which cleared on coughing. X-ray of the lung revealed no change from previous films. Tuberculin skin tests were negative.

Following a control period of nineteen days ACTH, 100 mg. daily, was begun and continued at this dosage for fifteen days. Because of the persistence of eosinophils in the blood, the dose of ACTH was increased to 160 mg. daily for twelve days. The dose was then gradually reduced over three days before cessation of therapy.

By the second week of ACTH administration the cough and sputum had disappeared. The patient was able to climb four flights of stairs without dyspnea. Behavior became increasingly excitable.

Following discontinuance of ACTH on the fiftieth day of study the patient was observed for seven days during which time the hyperexcitability disappeared. The improvement in respiratory symptoms persisted. On the fifty-seventh day of study cortisone, 200 mg. daily, was administered and continued for five days in order to observe the alterations in the chemical corticoids. The patient was discharged on the sixty-fourth day of study. At no time during the study did the appearance of the chest x-rays alter.

RESULTS

Beryllium Granulomatosis

Clinical Response. Adrenocorticotropic hormone (ACTH) was administered to two patients with chronic beryllium granulomatosis. Case 1 (L. H.) had had the disease for two and a half years. In patient B. W., with a history of three and a half years, the disease was considered more advanced. Both patients experienced a marked subjective and objective improvement. There was an increased feeling of well being, increased strength, and an increase in the depth of respirations. Exertion no longer produced undue dyspnea, although before treatment marked dyspnea would occur on even mild exertion.

The pulse was normal and the cough nonproductive in patient L. H. before ACTH. The respirations were 22 per minute and during therapy decreased to normal. In

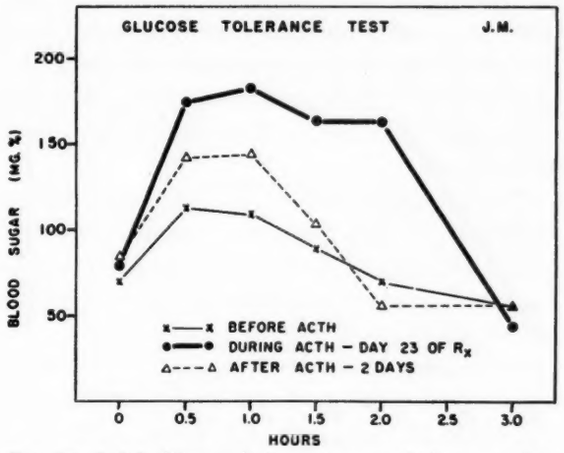


FIG. 20. J. M. (Case 11), impairment of glucose tolerance during ACTH administration.

B. W. the pulse was 120 per minute, respirations 28 per minute and 50 to 350 cc. of sputum were measured daily in the control period. During the first course of ACTH the pulse decreased to 70 per minute, the respirations to 12–16 per minute and the cough and sputum disappeared. (Fig. 10.) On withdrawing ACTH the improvements regressed but were re-established during a second course of the hormone. On completion of the second course of the hormone the pulse returned to 120 per minute, the respirations were 22 per minute but the sputum volume remained less than 50 cc. daily.

Both patients experienced severe symptoms following cessation of ACTH consisting of fatigue, weakness and spiking fever. (Figs. 6 and 14.) These symptoms disappeared after three weeks. In view of the flat glucose tolerance curve and low urinary corticoids demonstrated in this period in B. W., the reaction was considered to be possibly a temporary adrenal insufficiency. These symptoms were apparently not due to potassium deficiency since the serum potassium at this time was normal in L. H., and although slightly below normal in B. W.

the serum potassium following ACTH therapy was higher than previous values. It might also be postulated that a temporary exacerbation of the beryllium granulomatosis had occurred. The onset of this disease following pregnancy has suggested a possible hormonal relationship.[4,5] The termination of pregnancy and the corresponding decline in adrenal hormones or the cessation of ACTH administration may establish conditions leading to the manifestations of this disease.

Two months after ACTH was discontinued L. H. had maintained some improvement. In contrast to this, within three weeks B. W. had nearly reverted to the status before therapy.

Respiratory Function Studies. The vital capacity in both patients was markedly reduced. In L. H. it was 58 per cent (2404 cc.) of the predicted normal (4,144 cc.), and in B. W., 35 per cent (1,409 cc.) of the predicted normal (3,992 cc.). (Figs. 2 and 10.) On improvement these increased to 91 and 55 per cent of the predicted normal, respectively. The vital capacity was greatest during ACTH administration in both cases. On cessation of therapy the vital capacity decreased but remained higher than the original values.

The maximum breathing capacity determinations paralleled the vital capacity tests. (Figs. 2 and 10.) An improvement occurred during therapy and a return toward pre-treatment values was noted on cessation of ACTH. Patient B. W., clinically regarded as having a more advanced disease process, had a maximum breathing capacity of 80 per cent (80.3 L.) of the predicted normal (100.5 L.), and L. H. only 58 per cent (70 L.) of the predicted normal (120 L.). During ACTH therapy the values were 106 per cent (106.3 L.) and 115 per cent (139 L.) of the predicted normal, respectively.

The residual air in patient L. H. initially was 52.9 per cent of the total lung volume (5,050 cc.). During ACTH therapy the residual air decreased to 24.5 and 23.9 per cent eight days after discontinuing treatment. (Fig. 8.) It increased to 41.1 per cent fifty-seven days later. The reserve air in this same patient increased nearly 1,000 cc. during the period of study.

The index of alveolar mixing was high in patient L. H., but on improvement during ACTH therapy decreased from 10 per cent to the normal value of 2.5 per cent. (Fig. 8.)

The lung volume studies in patient B. W. were unusual. (Fig. 8.) The total lung volume (2,600 cc.) was markedly diminished. The residual air was 40.4 per cent of the total lung volume, but the absolute value (1,050 cc.) was that of the predicted normal residual air (1,000 cc.). During ACTH administration the total lung volume increased 900 cc. Of this, the complemental air increased 550 cc. and the residual air increased 350 cc. The residual air, however, continued to be 40 per cent of the total lung volume. There was no alteration in the reserve air which was diminished.

Breath holding on inspiration in B. W. increased from 15 seconds to 52 seconds during ACTH therapy. A rapid decrease followed cessation of the hormone. (Fig. 10.)

The ventilation efficiency was determined in both patients. The ventilation equivalent for oxygen represents the volume of air (in L.) that must be inspired to give up 100 cc. of oxygen to the body.[37] In normal individuals this value is seldom over 3 L. With exercise it does not tend to change as the minute volume of respiration and the oxygen consumed per minute increase in a parallel manner.[38] In patient L. H. there was a decrease toward normal of the ventilatory equivalent during ACTH administration and by the fifth post-treatment day. This was also true during exercise. Patient B. W. demonstrated a decrease in ventilation equivalent while receiving ACTH, but a return toward pre-treatment values between courses of ACTH. (Table 1.)

Psychiatric Observations. It was evident during the control period that in patient L. H. there was a successful repression of considerable aggression and hostility of which the patient was unaware. During the third week of ACTH administration there

were manifestations of mild aggressiveness and indirect expressions of hostility. The patient was more reactive to personal relationships. In addition, there was considerable elation over the improvement in physical symptoms. The patient was disturbed by the increased intensity of these aggressive and hostile tendencies. A reaction of severe anxiety to a near panic state followed and continued during the fourth week of therapy. The patient became increasingly apprehensive and worried and feared self-damage. A fear of the hormone developed. On the twenty-eighth day of administration the ACTH was discontinued. The anxiety, apprehension and fearfulness disappeared in two days although some aggressiveness persisted for two weeks. Psychologic tests mirrored the increase of aggressiveness and hostility demonstrated clinically.

B. W. was a man of superior intellectual capacity who showed much introversion, insecurity, silent hostility and was inhibited in actions. The reactions to ACTH administration were those experienced by a patient improving after a severe physical disease; he became more jovial and expressive.

It appears that ACTH produces a specific effect on emotional behavior, but the external manifestations of this vary according to the type of personality structure involved in each case. The occurrence of an organic neurologic reaction related to the physiologic changes also has been considered.[38]

Metabolic Study. Metabolic data demonstrated changes previously recorded in patients receiving adrenocorticotropic hormone.[39–41] In addition chemical findings characteristic of beryllium granulomatosis were observed. Urinary creatinine determinations indicate the completeness of the twenty-four-hour urine collections. (Figs. 4 and 12.)

Hematologic Study. A secondary polycythemia was demonstrated in each patient.[5] The hemoglobin in L. H. was 18.4 gm. and the hematocrit, 53.5 per cent. In B. W. the hemoglobin was 16.5 gm. and hematocrit, 46 per cent. (Figs. 3 and 11.) Bone marrow aspirations revealed a marked normoblastic hyperplasia of the marrow in both patients. During the period of study and ACTH administration there was a decrease in the hemoglobin and hematocrit, the lowest value in patient L. H. being 14.8 gm. of hemoglobin and hematocrit, 43 per cent.

TABLE 1
VENTILATION EQUIVALENTS

Patient	Day of Study	Stage of Treatment	Ventilation Equivalent (L.)	
			At Rest	Exercise
L. H.	15	Before ACTH	4.56	5.29
	29	During ACTH (14th day)	3.97	3.63
	43	During ACTH (28th day)	4.00	3.34
	48	After ACTH	3.51	3.22
B. W.	5	Before ACTH	4.67	....
	19	Before ACTH	3.81	4.22
	33	During ACTH (14th day of first course)	3.33	....
	61	After ACTH (after second course)	4.06	4.31
	82	During ACTH (5th day of third course)	3.84	3.55
J. M. (Silicosis)	18	Before ACTH	2.83	3.15
	32	During ACTH	2.84	2.50
Normals	L. B.	.....	2.62	2.74
	P. P.	.....	2.87	2.38
	R. S.	.....	....	3.00

In B. W. the hemoglobin fell to 11.1 gm. and the hematocrit to 36 per cent. This decrease was in large part due to hemodilution from fluid retention. Following cessation of ACTH there was a simultaneous diuresis and hemoconcentration. In addition the large volume of blood drawn for chemical determinations in patient B. W. may have contributed to the diminution of red cells.

During administration of ACTH there was a leukocytosis, the white blood cell count reaching 18,300 in L. H. and 18,700 in B. W. This leukocytosis disappeared following cessation of therapy. (Figs. 3 and 11.)[42]

The direct eosinophile count was em-

ployed as a measure of adrenal function in order to determine an adequate ACTH dosage.[43] In both cases there was a decrease to zero during ACTH therapy. A rise occurred as the dose of ACTH was reduced from 100 mg. daily. (Figs. 3 and 11.)

The sedimentation rate has been reported to be normal in beryllium granulomatosis.[5,7] The sedimentation rate in L. H. was normal at the onset of study but the values during ACTH were lower than in the control period. The reaction in the post-treatment period was accompanied by an elevation of the sedimentation rate to above normal levels. In B. W., however, the sedimentation rate was elevated initially and decreased to normal during ACTH. A rise occurred on cessation of the hormone. (Figs. 6 and 14.)

17-*Ketosteroids.* In all three cases the urinary 17-ketosteroids during the control periods ranged below values observed in normal adult males. The response to ACTH therapy varied somewhat in the different patients. In L. H. there was a gradual increase in the excretion of 17-ketosteroids which reached a maximum level during the second week of therapy. With continued treatment at the same dose level the 17-ketosteroids decreased, and on cessation of treatment fell below the initial control level. Eight days later they returned to control values. (Fig. 3.) In J. M., the case of silicosis, the increase with ACTH therapy was less marked and the 17-ketosteroids did not fall below the control level on withdrawal of the hormone. (Fig. 16.) B. W. showed a lag in response of six days during the first course of treatment with ACTH, but in the second course a prompt rise occurred the first day, reaching a peak of 66 mg. per twenty-four hours in eight days. (Fig. 11.)

Corticoids. Urinary corticoids were determined by two methods, a biologic and a chemical assay. The former method measures only those adrenal steroids capable of affecting carbohydrate metabolism, while the latter includes all metabolites having an alpha-ketol grouping at C_{20-21}. In all three patients the administration of ACTH caused a marked rise in both the glucocorticoids and the chemical corticoids. (Figs. 3, 11 and 16.) In B. W. there was an immediate increase in the output of glucocorticoids at the onset of ACTH at a time when no response in the 17-ketosteroid excretion had occurred. When the dose of ACTH was lowered at the end of therapy, the chemical corticoids fell promptly and were actually below the level observed during the control period. A flat glucose tolerance curve was obtained at that time. (Figs. 11 and 15.)

The administration of 200 mg. of cortisone daily in J. M., the silicosis patient, was accompanied by an increase in chemical corticoids, similar in rate and amount to that noted during ACTH therapy. However, there was no rise in the 17-ketosteroids. (Fig. 16.)

Electrolytes. Adrenocorticotropic hormone administration is accompanied by retention of sodium and chloride with associated fluid retention, increase in body weight and potassium loss.[40] These patients received approximately 130 mEq. of sodium and 102 mEq. of potassium daily in the diet.

A decrease in urine volume and increase in urine specific gravity was noted at the onset of ACTH administration in each patient. Despite a constant fluid intake during therapy in patient L. H., the urine volume increased and the specific gravity decreased to pre-treatment values. This suggests that the water-retaining effect tends to wear off. On reduction of the dose or on discontinuing ACTH there was a marked increase in urine volume and decrease of specific gravity. (Figs. 5 and 13.) As a result of this fluid retention L. H. gained 2 kg. in weight during the first week of ACTH. B. W., however, retained fluid more readily, gaining 6 kg. of weight during one course of ACTH, concomitant with the appearance of edema of the legs and genitalia. A rapid diuresis and weight loss followed cessation of ACTH. (Fig. 12.)

During ACTH therapy there was a decrease in excretion of urinary sodium and chloride. (Figs. 5 and 13.) As the dose of the

hormone was reduced and on cessation of ACTH, there was a marked increase of urinary sodium and chloride. In patient B. W. the day following completion of the first course of ACTH the urinary sodium was 685 mEq. in twenty-four hours, the control values having been approximately 150 mEq. per twenty-four hours.

The urinary chloride followed a trend similar to that of the sodium. There was an apparent retention of chloride during ACTH administration, and an increased excretion on reduction of the dose or on discontinuing the hormone. The control values in patient B. W. were 100 to 200 mEq. of urinary chloride daily. On discontinuing ACTH 626 mEq. were excreted in twenty-four hours.

Potassium excretion in the urine increased considerably in patient L. H. throughout the course of ACTH. (Fig. 5.) Although the serum potassium was low initially, it decreased to 3.6 mEq. per L. on the last day of treatment. Concomitantly there was a slight rise of the carbon dioxide combining power from 22.5 mEq. per L. to 26.2 mEq. per liter. B. W. did not show as marked a loss of potassium in the urine. (Fig. 13.) The serum potassium, however, decreased from 5.3 to 3.4 mEq. per L., and the carbon dioxide combining power rose from 19.4 to 32.2 mEq. per L. There also was a slight reduction of the serum chloride to 95.5 mEq. per L.

Both demonstrated the tendency of patients receiving ACTH to develop hypopotassemic, hypochloremic alkalosis.[41] Despite the marked retention of fluid in one patient (B. W.) no complications occurred.

Nitrogen Metabolism. Beryllium granulomatosis is characterized by weight loss and cachexia.[5] Nitrogen balance studies were conducted to compare these patients to those having chronic debilitating diseases previously studied.[44] The initial diet consisted of 12.6 gm. of nitrogen and 2,300 calories. During the control period patient L. H. excreted 11 gm. of nitrogen daily, resulting in a positive nitrogen balance of approximately 1.5 gm. (Fig. 4.) On ACTH administration the nitrogen excretion increased to 19 gm. daily with a negative nitrogen balance of 6.4 gm. This increased nitrogen excretion and resultant negative nitrogen balance persisted throughout the period of treatment. A loss of 2.9 kg. of the initial body weight occurred. In the post-treatment period the nitrogen excretion was 12.5 gm. daily and nitrogen equilibrium was established. Later the daily nitrogen intake was increased to 24 gm. Whereas the nitrogen excretion continued to be 12.5 gm., a positive nitrogen balance of approximately 11.5 gm. was demonstrated. This response is similar to that of chronically debilitated individuals.

Patient B. W. received 12.6 gm. of nitrogen in the diet daily during the control period. The nitrogen excretion was 10.6 gm. resulting in a positive nitrogen balance of 2 gm. During the control phase the nitrogen intake was increased to 24 gm. without altering the caloric intake. The nitrogen excretion increased to 15 gm. and the nitrogen balance was plus 9 gm. The initial diet was then resumed and ACTH administered. Although on a lower nitrogen intake, the nitrogen excretion continued to be 15 gm., resulting in a negative nitrogen balance of 2.4 gm. (Fig. 12.)

During the second course of ACTH while the patient was again in negative nitrogen balance, the nitrogen intake was doubled (24 gm. daily). The nitrogen excretion increased to 19 gm., resulting in a positive nitrogen balance of 5 gm. daily. After ACTH was discontinued the patient was maintained on a diet with 16 gm. of nitrogen. The nitrogen excretion was 12 gm. daily and a positive nitrogen balance of 4 gm. occurred. Little change in nitrogen excretion was attained by increasing the nitrogen intake to 24 gm. daily, but the nitrogen balance increased to plus 11 gm. A weight gain of 1.4 kg. occurred over a three-week interval. A third course of ACTH while the patient was on this high protein diet, resulted in an increase of nitrogen excretion to 18 gm., but a positive nitrogen balance of 6 gm. persisted.

This study demonstrates that the administration of ACTH produces an increased nitrogen excretion, but that with a sufficient protein intake a negative nitrogen balance need not occur. The influences tending to store nitrogen in chronic debilitated patients were not abolished by ACTH. Furthermore, patients with beryllium granulomatosis react as do other patients with chronic debilitating diseases, and on a high protein intake can be maintained in positive nitrogen balance.

TABLE II
CASE I—PATIENT L. H.

Day of Study	ACTH* (mg.)	Thymol Turbidity (units)	Thymol Flocculation	Cephalin Flocculation	Calcium†		Urinary Beryllium (micrograms)
					Serum (mg. %)	Urine (mg./24 hr.)	
		‡less than 4	0–1+	0–1±	9–11	60–100	0
1		7.45	3+	1+	9.4		
6						185	
7						185	
10						262	
11						262	
16	100				10.2		
19	100	6.1	3+	0			
20	100					247	
23	100	5.95	4+	0	10.0		0
26	100					296	
29	100	1.6	4+	0	10.9		
31	100					152	
32	100	4.5	1+	0			
39	100	3.7	2+	0			
43	20					358	
45							0.14
46						121	
51					10.9		
52							0
54					10.1		
108		8.8	5+	0			

* ACTH was administered from the sixteenth day through the forty-third day.
† Daily calcium intake was 200 mg.
‡ This horizontal line of figures represents normal values.

Serum Proteins. The serum globulin in beryllium granulomatosis has been reported to be slightly elevated[5] or normal.[7] Whether this elevation is the result of hepatic cell damage or an abnormality of protein metabolism is not known. Both patients had slightly elevated serum globulin. During administration of ACTH this decreased from 3.9 to 2.4 gm. per cent in B. W., and from 3.7 to 1.1 gm. per cent in L. H. There was a concomitant diminution in the total protein. (Figs. 4 and 12.) This decrease was not due to hemodilution since these low levels persisted after diuresis had occurred on cessation of ACTH. Later the serum globulin increased to pre-treatment values. Since both patients had evidence of liver damage, the trend toward normal of serum proteins during ACTH administration may have been the result of improved hepatic function. However, a decrease of serum globulin in patients without detectable liver disease has occurred.[39,41]

TABLE III
PATIENT B. W.—LIVER FUNCTION TESTS

Day of Study	ACTH*	Thymol Turbidity	Thymol Flocculation	Cephalin Flocculation
1		12.6	5 plus	trace
18		9.7	5 plus	1 plus
20	ACTH begun			
29	ACTH	5.35	2 plus	0
34	ACTH stopped			
36		4.3	3 plus	0
40	ACTH begun			
43	ACTH	4.9	2 plus	0
50	ACTH	2.9	1 plus	0
52	ACTH stopped			
57		2.65	0	0
61		2.65	0	0
71		6.6	trace	0
78		8.1	0	1 plus

* ACTH was administered from the twentieth through the thirty-fourth day, and from the fortieth through the fifty-second day.

Liver Function Tests. Granulomatous lesions, cellular infiltration and congestion of the liver occur in chronic beryllium granulomatosis.[8] Cephalin flocculation tests were normal throughout the study in both patients. Thymol turbidity was 7.45 units and the thymol flocculation test 3 plus in patient L. H. In B. W. the thymol turbidity was 12.6 units and the thymol flocculation 5 plus. During the administration of ACTH these values decreased to normal, but on discontinuance of the hormone reverted to previous abnormal values. (Tables II and III.) Since these tests are frequently positive when the serum globulin is elevated, the improvement may merely reflect that alter-

ation noted in the serum protein. However, the changes may be attributable to the improvement in pulmonary function and resultant decrease in hepatic congestion.

Uric Acid. Adrenocorticotropic hormone causes an increased excretion of urinary uric acid and diminution of the serum uric acid.[45] The serum uric acid in patient L. H. decreased from 5.2 to 1.1 mg. per cent during ACTH administration. In B. W. it fell from 5.6 to 1.2 mg. per cent. An increase was noted on cessation of therapy. Concomitant with these falls was an increase in the urinary excretion of uric acid. (Figs. 4 and 12.)

Vitamin C. The diminished excretion of vitamin C following trauma[46] and the apparent relationship between pituitary activity and the concentration of vitamin C in the adrenal gland[47] prompted the investigation of vitamin C metabolism in patients receiving ACTH.

Each patient received a supplement of 250 mg. of vitamin C daily. After establishment of this level of intake in B. W. a rise of vitamin C excretion occurred abruptly eight days later in the control period. A sharp increase of urinary vitamin C at the onset of each course of ACTH was demonstrated. (Fig. 14.) This is consistent with studies of other patients.[39] On each cessation of therapy there was a rapid, temporary diminution of vitamin C excretion followed by an increase. Patient L. H. demonstrated no rise in the control period, but the urinary vitamin C increased the fourth day of ACTH and remained elevated during the entire course of therapy. Cessation of ACTH was followed by a temporary overswing to lower vitamin C excretion as seen in B. W. (Fig. 6.) The blood vitamin C tended to parallel the changes noted in the urine, but insufficient data are presented to draw further conclusions.

Cholesterol. Total cholesterol determinations in patient L. H. demonstrated no alteration from normal during ACTH administration. However, there was an increase to 298 mg. per cent following cessation of therapy. (Fig. 6.)

In B. W. the total cholesterol remained constant throughout the study. The cholesterol ester, however, diminished 35 and 48 mg. per cent during two periods of ACTH injection. (Fig. 14.)

Glucose Metabolism. Impaired carbohydrate metabolism has been induced by ACTH in that impaired glucose tolerance curves and glycosuria occur.[48] Patient L. H. developed glycosuria and an impaired glucose tolerance during ACTH administration. (Figs. 6 and 7.) This intolerance of glucose disappeared on cessation of therapy.

B. W. demonstrated a more marked impairment of the glucose tolerance during therapy but no glucosuria. (Fig. 15.) One day following cessation of the second course of therapy the glucose tolerance curve was flat, suggestive of an adrenal insufficiency coinciding with the development of the clinical reaction previously described and the low corticoid values.

Glutathione. A decreasing concentration of the blood glutathione during ACTH has been reported.[49] Patient L. H. demonstrated an increase from 15 to 33 mg. per cent and B. W. decreased from 28 to 19 mg. per cent during ACTH administration. (Figs. 6 and 14.) The trend in blood glutathione has not been consistent during ACTH therapy.[39]

Calcium. Elevated blood calcium, hypercalcuria and renal stones occasionally occur in beryllium granulomatosis.[5] Patient L. H. received 200 mg. of calcium in the diet daily. Hypercalcuria was present, 262 mg. of calcium being measured in one twenty-four-hour period. Only occasional urinary calcium determinations were carried out. (Table II.) During the course of ACTH hypercalcuria continued. One analysis following cessation of therapy revealed a lower value of 121 mg. per twenty-four hours. The serum calcium remained normal. Further studies are necessary to determine whether or not there is a reduction in the excretion of calcium as a result of ACTH therapy.

Beryllium Analysis. Beryllium has been measured in the urine of persons exposed to beryllium dusts and in patients with beryl-

lium granulomatosis.[49] People not exposed to beryllium do not excrete detectable amounts in the urine. However, workers in beryllium industries may excrete this metal although no sign of the disease can be demonstrated. Approximately 0.3 microgram of beryllium was detected in one twenty-four-hour urine specimen of patient B. W. In L. H. none was detected during the administration of ACTH. However, the day following cessation of ACTH, 0.14 microgram of beryllium was detected. Seven days later another analysis revealed no beryllium. (Table II.)

Beryllium occasionally occurs in the urine of patients who on most occasions do not excrete it. The number of determinations in this study are too few to allow any conclusions. However, the question is raised as to whether or not ACTH brings about mobilization of beryllium or causes an increased excretion of the metal.

Comment. Remissions in beryllium granulomatosis have not occurred with the use of other agents, and regressions such as demonstrated in these patients are unlikely to occur spontaneously.[50,51] The temporary improvement during ACTH administration suggests that this disease is reversible.

It has been postulated that since the pulmonary lesions are characterized in part by a lymphocytic infiltration, the improvement observed may be the result of destruction of these cells. Discontinuance of ACTH may be followed by a return of the infiltration. Furthermore, resolution of fibrosis may occur.[1] Whether or not the beryllium in the tissues can be fully mobilized and excreted is uncertain. Other modes of therapy have not succeeded in doing this.[52]

It would appear that repeated short courses of ACTH would produce fewer complications than prolonged therapy. Prolonged cortisone administration may be of value.

Obviously further studies in regard to the alterations of respiratory function, beryllium excretion and method of ACTH administration are desirable.

Silicosis

Metabolic and respiratory function studies were carried out on a patient with silicosis of four years' duration.

Clinical Response. During the administration of ACTH for thirty days this patient experienced an increased feeling of well being, increased strength, a diminution of dyspnea on exertion and an increased ease of respiration. Cough and the sputum volume of 20 to 50 cc. daily disappeared. (Fig. 19.) During the second week of therapy hyperexcitability, of which the patient was aware, developed. Following discontinuance of therapy this hyperexcitability diminished but the patient remained improved.

Respiratory Function Studies. The vital capacity increased from 58 per cent (2,487 cc.) of the predicted normal (4,274 cc.) to 74 per cent (3,150 cc.). A parallel improvement in maximum breathing capacity from 70 per cent (90.7 L.) of the predicted normal to 100 per cent (129.6 L.) was observed. (Fig. 19.) Breath holding on inspiration and expiration was doubled during ACTH therapy. There was minimal alteration in the residual air determinations, though the alveolar index of mixing decreased from 4 to 2 per cent. (Fig. 8.) There was no significant deviation from the expected normal in measurements of the ventilatory efficiency either before or during treatment. (Table I.)

Metabolic Data. A secondary polycythemia was present. (Fig. 16.) The hemoglobin was 16.2 gm. and the hematocrit 46.5 per cent. During ACTH administration there was a decrease to 12.8 gm. of hemoglobin and 39.5 per cent hematocrit concomitant with fluid retention. Cessation of therapy was followed by diuresis and hemoconcentration, the hemoglobin rising to 17.9 gm. and the hematocrit to 52 per cent. A slight elevation of the white blood cell count from 7,000 to 13,500 occurred during ACTH therapy. An initially elevated sedimentation rate of 33 mm. per hour decreased to zero but rose again when the drug was discontinued. (Fig. 18.)

The eosinophils diminished when ACTH was given but never completely disappeared. (Fig. 16.) After two weeks of ACTH the eosinophils increased in the peripheral blood. Hence, the dose of ACTH was increased from 100 mg. to 160 mg. daily in view of a possible escape from the effect of the hormone. A second decrease occurred but again not to zero.

The 17-ketosteroids and urinary corticoids have been discussed in conjunction with the patients with beryllium granulomatosis.

At the onset of ACTH therapy there was a reduction in urine volume, an increase in urine specific gravity and a 5 kg. weight gain. On cessation of therapy there was a diuresis and simultaneous weight loss. Retention of fluid and weight gain of 3 kg. reoccurred with the administration of cortisone for five days. The serum potassium decreased from 5.0 to 3.7 mEq./L. at the end of the second week of ACTH therapy, but no further decrease occurred during the subsequent two weeks of treatment. (Fig. 18.)

The nitrogen balance findings were similar to those of debilitated patients. (Fig. 17.) On an intake of 16 gm. of nitrogen the nitrogen excretion was 15 gm. daily during the control period, resulting in a positive nitrogen balance of 1 gm. When the intake was increased to 24 gm. daily, the nitrogen excretion remained 15 gm. and a positive nitrogen balance of 9 gm. resulted. With administration of ACTH the nitrogen excretion increased to 22 gm. but a positive balance of 2 gm. was usually maintained. An increase of the intake to 32 gm. of nitrogen, while ACTH was still being administered, resulted in a further increase of nitrogen excretion to 30 gm. and the positive nitrogen balance of 2 gm. persisted. Following discontinuance of ACTH and maintenance of an intake of 32 gm. of nitrogen, the nitrogen excretion fell to 26 gm. daily, and 6 gm. of nitrogen were stored daily. This demonstrates that ACTH increased the nitrogen excretion, but on a sufficiently high protein intake did not necessarily produce a negative nitrogen balance.

The serum globulin was 4.8 gm. per cent and the total protein 9.1 gm. per cent. During ACTH therapy the globulin decreased to 1.6 gm. per cent with a concomitant decrease of the total protein to 5.5 gm. per cent. (Fig. 17.)

The initial serum uric acid was 5.0 mg. per cent and decreased to 2.3 mg. per cent when ACTH was given. A simultaneous rise of the urine uric acid was noted as in the previous patients. (Fig. 17.)

This patient appeared to be depleted of vitamin C since none was detected in the urine during the control period. (Fig. 18.) No vitamin C supplement was administered. During ACTH therapy there was a slight increase, but not to values seen in other patients.[39] Minimal amounts of vitamin C were detected in the urine following cessation of ACTH and none during five days of cortisone therapy.

No glycosuria occurred while ACTH was administered. A glucose tolerance curve was normal after fifteen days of ACTH, but by the twenty-second day of therapy, there was a definite impairment of tolerance. (Fig. 20.) The blood glutathione was noted to decrease during the period of therapy and did not rise after the cessation of ACTH. (Fig. 18.)

Comment. The period of observation is too short to determine how long the improvement will persist after cessation of therapy. The appearance of the chest x-rays was unaltered by treatment. Since there has been no adequate treatment for silicosis,[51] further investigation of the effect of ACTH in this disease is indicated.

SUMMARY

1. Adrenocorticotropic hormone (ACTH) was administered to two patients with chronic beryllium granulomatosis. Temporary, subjective and objective improvement occurred as judged by respiratory function studies and x-rays.

2. Improvement was demonstrated in one patient with silicosis on administration of ACTH.

3. Metabolic observations of the effects of

adrenocorticotropic hormone in these patients are presented.

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Effects of Cortisone and ACTH in Cases of Chronic Pulmonary Disease with Impairment of Alveolar-capillary Diffusion*

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IT is the purpose of this paper to report the effect of adrenocorticotropic hormone (ACTH) and cortisone upon the course of three patients suffering from pulmonary insufficiency due to impaired alveolar-capillary function and to illustrate the application of certain special methods of measurement in assaying the results of therapy.

Baldwin, Cournand and Richards[1] in their studies of pulmonary fibrosis have presented detailed observations in fourteen patients in whom the physiologic findings suggested that impaired alveolar-capillary function was the basis of the pulmonary insufficiency observed. Clinical diagnoses included pulmonary scleroderma, carcinoma with lymphangitic pulmonary metastases, pulmonary fibrosis following inhalation of sulfur dioxide and pulmonary granulomatosis of unknown etiology. This group was characterized clinically by severe dyspnea on exertion and often at rest, by weakness, lassitude and a dry hacking cough. Clubbing of the digits was not infrequent.

Physiologic findings common to the group included reduction in lung volume with relative preservation of the maximum breathing capacity, extreme hyperventilation at rest and on exercise and arterial oxygen unsaturation after exercise and sometimes at rest. Others have reported this syndrome in association with pulmonary granulomatosis secondary to beryllium poisoning[2,3] and, more recently, eight additional patients with this syndrome have been studied by Austrian et al.[4]

The histologic appearance of the lungs in the cases examined has supported the contention that there is impaired alveolar-capillary function in this type of pulmonary insufficiency.[1,2]

Until recently therapy of these conditions has been entirely of a supportive nature, supplementary oxygen being the only agent which has afforded relief. ACTH has been reported to have an inhibitory effect upon the development of granulation tissue;[5] hence it might be expected to have some effect upon pulmonary insufficiency resulting from pulmonary granulomatosis. Kennedy et al.[6] have reported the effect of ACTH upon the course of a patient with pulmonary insufficiency secondary to beryllium granulomatosis. In addition to striking clinical improvement there was improvement in the lung volumes, maximum breathing capacity and in the roentgen appearance of the lungs.

The three patients presented herein had clinical and physiologic findings suggesting alveolar-capillary dysfunction. The diagnoses were varied: one patient was thought to have pulmonary scleroderma, one was

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shown to have pulmonary granulomatosis and the third remained undiagnosed.

METHODS

Technics used in the measurement of the lung volumes, maximum breathing capacity, ventilation and arterial blood gas values have been described elsewhere.[7] Other methods used in this report were those developed by Riley et al.[8] which make possible a fairly precise delineation of the degree and nature of alveolar-capillary dysfunction in patients with pulmonary disease by (1) determination of the oxygen-diffusing capacity of the lungs and (2) measurement of disturbances in ventilation-perfusion relationships in the lungs. Cournand, Riley et al.[9] have reported on the usefulness of these methods in studies of the effects of therapy in a variety of pulmonary diseases.

The oxygen-diffusing capacity of the lungs is a measure of the permeability, with respect to oxygen, of the alveolar-capillary membrane. Diffusion of oxygen across the membrane is dependent upon the presence of a higher partial pressure of oxygen in alveolar air than in capillary blood. The difference in oxygen pressure or gradient of pressure existing between alveolar air and capillary blood is largest just as the mixed venous blood enters the capillary. The diffusion of oxygen from the alveolus to the blood causes the oxygen pressures on each side of the membrane to approach each other; hence the gradient continuously decreases as oxygen is absorbed. By means of the aforementioned methods[8] one can calculate a theoretic *mean pressure gradient* which, were it present continuously along the pulmonary capillary, would result in the same oxygen absorption as actually does occur with the existing, progressively changing gradient from arterial to venous end of the capillary. The oxygen intake per minute divided by this theoretic *mean pressure gradient* is the *oxygen-diffusing capacity*. At rest this value is normally greater than 15 cc. of oxygen per minute per mm. Hg of *mean pressure gradient*.

Disturbances in ventilation-perfusion relationships in the lungs consist in the ventilation of poorly perfused alveoli and the perfusion of poorly ventilated alveoli. The ventilation of poorly perfused alveoli resembles in its effect upon the expired air the ventilation of the anatomic dead space in that it tends to make the composition of expired air more nearly like that of the inspired air. This effect of the ventilation of the anatomic dead space and of the poorly perfused alveoli can be expressed quantitatively by determining the *physiologic dead space*, using the Bohr equation. This determination is facilitated by substituting the partial pressure of carbon dioxide in arterial blood for the partial pressure of carbon dioxide in alveolar air, the two values being equal in all but a few instances.[10] The physiologic dead space is not considered abnormally large in this laboratory unless it exceeds 30 per cent of the tidal air.

The perfusion of poorly ventilated alveoli resembles, in its effect upon the arterial blood, a true venoarterial shunt in that it tends to make the composition of arterial blood more nearly like that of mixed venous blood. The total effect, then, of small anatomic shunts plus an increase in the number of poorly ventilated although well perfused alveoli can be expressed as being equivalent to the effect of a true shunt of a certain magnitude. The amount of this calculated shunt when expressed as a fraction of the total pulmonary blood flow is termed the *physiologic venous admixture*. Normally this value does not exceed 6 per cent.

If the alveolar-capillary membrane is altered in some areas to such a degree that no gas exchange can take place, the ventilation of the alveoli concerned will contribute to the physiologic dead space and the perfusion of these alveoli will contribute to the physiologic venous admixture no matter how well ventilated these alveoli are.

Measurement of the oxygen-diffusing capacity and the physiologic venous admixture requires determination of the oxygen intake per minute and of the partial pressures of oxygen and carbon dioxide in the

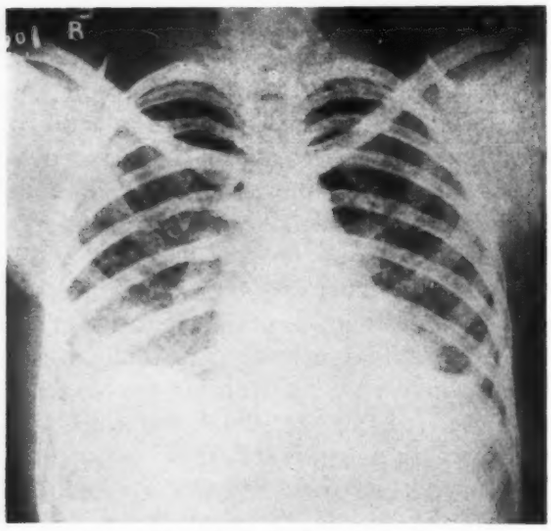


FIG. 1. X-ray of the chest of patient M. M., Case I, with generalized scleroderma.

arterial as well as in the mixed venous blood at two different levels of oxygenation of the arterial blood. This is accomplished by having the patient breathe in succession air of two compositions, one having a higher oxygen percentage than the other. The greatest degree of accuracy in these determinations is secured if the patient remains in a steady metabolic state at both levels of oxygenation.

CASE REPORTS

CASE I. M. M., a twenty-two year old Negro woman, was first seen at Bellevue Hospital in May, 1948, complaining of easy fatigue and progressive skin changes. In the preceding two years she had noted depigmentation of the skin of her left scapular and peri-oral regions, and tightness of the skin over her hands and feet. During this time she had noted moderate dyspnea on exertion and a non-productive cough.

On physical examination the characteristic changes of scleroderma in the skin of the upper extremities and face were apparent. There were harsh breath sounds and fine rales over both lung fields. The heart was not enlarged. Its rhythm was regular. The second sound was markedly accentuated in the pulmonic area. No murmurs were heard. The remainder of the physical examination was not abnormal.

The hemoglobin and white blood cell count were normal. An x-ray of the chest (Fig. 1) showed fine reticular shadows throughout both lungs. A barium swallow demonstrated abnormal emptying of the esophagus. After physiologic studies (Table I) had been performed and a skin biopsy obtained, the patient was discharged from the hospital unimproved. The skin biopsy revealed flattening of the rete pegs and a marked increase in the collagen of the dermis. Elastic tissue fibers were decreased in number and were somewhat fragmented.

The patient was readmitted to Bellevue Hospital in May, 1949, for additional physiologic studies (Table II) at which time she reported no change in her symptoms and there was no detectable change in her physical condition. On January 12, 1950, cortisone acetate* therapy was begun, the dosage being 100 mg. per day intramuscularly until January 27, 1950, and 150 mg. per day from January 27 to January 31, 1950. After three days of treatment the skin of the fingers, dorsum of the hands and peri-oral regions was noted to be less indurated and more flexible. This improvement persisted during the period of treatment and was still present two months after the course of therapy had ended. Despite this change in the gross appearance of the skin there was no change in its histologic appearance judging from frequent biopsies taken during the course of treatment.

There was no change in the symptoms referable to the lungs or in their appearance by x-ray and there were no toxic manifestations observed from therapy. Physiologic studies were carried out at frequent intervals during the course of treatment. (Tables I and II.)

CASE II. E. H., a seventeen year old white male, entered Bellevue Hospital in November, 1949, because of increasing dyspnea on exertion. Following an acute respiratory illness in 1947 he had noted the gradual but steady progression of dyspnea on exertion and a non-productive cough. No history of exposure to any toxic substances could be elicited.

On physical examination the patient was seen to be poorly nourished and somewhat underdeveloped. Clubbing of the fingers was present. Small discrete lymph nodes were noted in both supraclavicular areas and in both axillas. The respiratory rate was slightly increased and a few rales were heard at the bases of both lungs. The heart was normal except for an accentuation of the second sound in the pulmonic area. The tip of the spleen was felt on one occasion. The remainder of the physical examination was not abnormal.

* Merck and Company, Inc., Rahway, N. J.

The hemoglobin and white blood cell count were normal. An x-ray of the chest (Fig. 2A) showed a fine, diffuse, reticular infiltration in both lungs and enlargement of the hilar and mediastinal lymph nodes.

On November 28, 1949, biopsy of an axillary lymph node was made. Sections of this node showed extensive replacement of the nodal tissue by fairly discrete granulomas made up of epithelioid cells and large numbers of giant cells. These giant cells were of the Langhans and foreign body types and many of them contained doubly refractile lamellated crystalline material.

On December 28, 1949, through a short anterior incision the right chest was opened and a portion of the cardiophrenic edge of the middle lobe was removed for biopsy. At this time the lung was noted to be pale, pink and moderately granular on its surface. Enlarged lymph nodes were noted at the hilum and in the horizontal fissure. One hilar node was removed for biopsy. This node had the same histologic appearance that had been observed in the axillary node. The section of the lung showed extensive disruption of pulmonary architecture by large numbers of more or less discrete interstitial granulomas, which showed the same combination of epithelioid cells, giant cells and doubly refractile crystalline material that had been found in the lymph nodes. (Fig. 3A.)

Physiologic studies were carried out in November, 1949, and February, 1950. (Tables I and II.) Beginning on March 10, 1950, 300 mg. of cortisone acetate were given intramuscularly on the first day, 200 mg. on the second and third days and then 100 mg. daily until April 15, 1950, for a total of 4.0 gm. Soon after cortisone was started the patient felt better, became more active about the ward, developed a voracious appetite, began to gain weight and noted some

TABLE I

DATA ON LUNG VOLUMES, MAXIMUM BREATHING CAPACITY, VENTILATION AND ARTERIAL OXYGEN SATURATION IN THREE CASES DISCUSSED HEREIN

Case	Date	Vital Capacity (per cent of Predicted)	Total Capacity (per cent of Predicted)	$\frac{RA}{TC} \times 100$*	Maximum Breathing Capacity (per cent of Predicted)	Ventilation, Liters per Minute per sq.m.b.s.		Arterial Oxygen Saturation, Per cent	
						Rest	Exercise	Rest	Exercise
I, M. M. (Generalized scleroderma)	7/ 7/48	33	37	33	86	5.7	16.1	96	79
	1/ 4/50	28	35	35	75	4.8	15.5	93	80
Cortisone therapy from 1/12/50	1/23/50	..	..	..	...	5.5	11.6	95	80
to 1/31/50	1/30/50	33	37	38	78	5.9	13.6	96	81
II, E. H. (Pulmonary granulomatosis)	11/23/49	51	58	28	89	7.8	24.5	92	86
	2/23/50	47	51	25	78	9.3	24.1	98	89
Cortisone therapy from 3/10/50	3/22/50	55	58	20	90	6.0	16.9	98	92
to 4/15/50	3/28/50	..	..	..	...	6.5	17.3	98	94
	4/ 4/50	53	59	18	76	....	....	..	..
	5/ 5/50	52	59	30	88	6.9	17.6	94	84
	5/18/50	53	60	18	99	6.8	17.6	94	81
III, G. M. (Undiagnosed pulmonary disease)	5/10/50	19	..	..	51	9.7†	....	70†	..
	5/12/50	..	..	..	...	10.7†	....	64†	..
ACTH therapy from 5/22/50 to	5/25/50	..	..	..	...	7.1	....	81	..
6/6/50	6/ 5/50	42	..	..	102	5.9	....	94	..
Cortisone therapy from 6/9/50	6/ 9/50	..	..	..	...	7.6	....	88	..
	6/19/50	..	..	..	...	5.8	....	96	..

* Abbreviations: $\frac{RA}{TC} \times 100$, ratio of residual air to total capacity expressed as per cent; sq.m.b.s., square meter of body surface area.

† These determinations were made while the patient was breathing 25% oxygen.

decrease in his dyspnea on exertion. He gained more than 20 pounds, had occasional glycosuria and developed a moon face and slight hirsutism. There were, however, no major toxic complications of cortisone treatment. X-ray of the chest taken three weeks after the beginning of therapy showed a slight but definite decrease in the hilar and mediastinal lymph node enlargement as well as a decrease in the reticular infiltration in the lung (Fig. 2B). Physiologic studies were repeated at frequent intervals during and after cortisone administration. (Tables I and II.)

TABLE II

DATA ON PHYSIOLOGIC DEAD SPACE, PHYSIOLOGIC VENOUS ADMIXTURE, OXYGEN-DIFFUSING CAPACITY, CARDIAC INDEX AND PULMONARY ARTERIAL PRESSURES IN THREE CASES DISCUSSED HEREIN

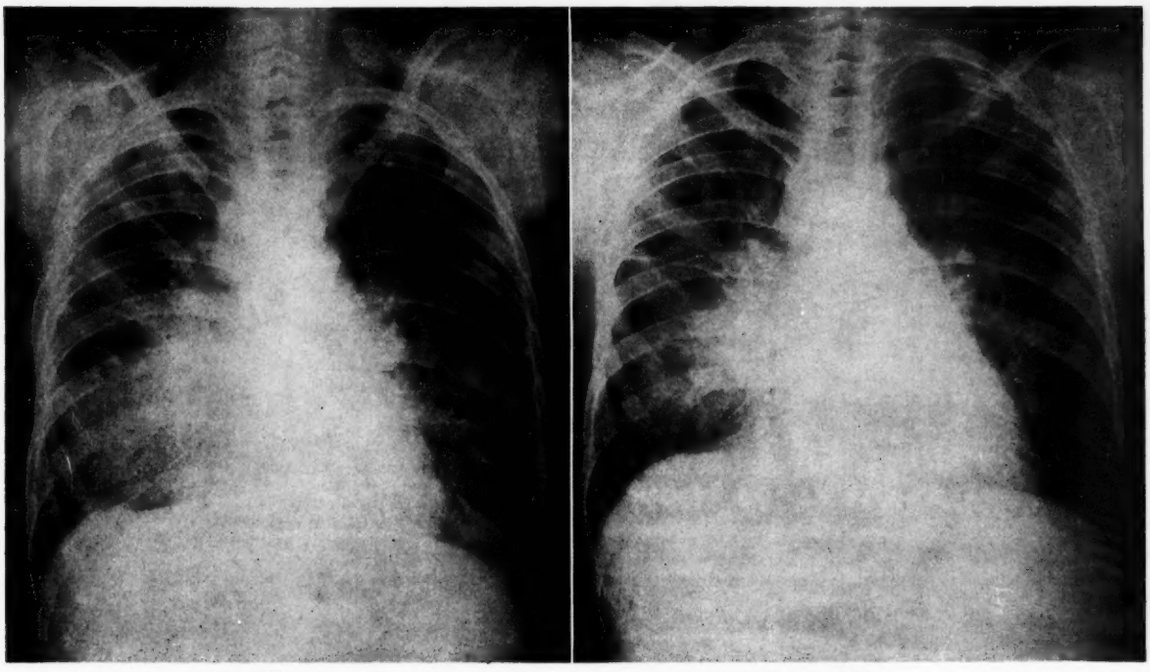
Case	Date	P.D.S.*	V.A.	Oxygen-diffusing Capacity†	Oxygen cons. cc. per Minute per sq.m.b.s.		Cardiac Index, Liters per Minute per sq.m.b.s.		Pulmonary Arterial Pressures, mm. Hg		Percentage of Oxygen in the High and Low Oxygen Mixtures
									s/d,m	s/d,m	
					H	L	H	L	H	L	
I, M. M. (Generalized scleroderma)	5/11/49	32	3	6	133	132	3.60	7.30	20/9, 13	41/18,27	H = 21, L = 14
Cortisone therapy from 1/12/50 to 1/31/50	1/30/50	36	5	5	141	132	3.71	3.37	29/12,19	47/20,31	H = 21, L = 16
II, E. H. (Pulmonary granulomatosis)	11/13/49	42	15	8	185	210	4.80	4.88	35/17,27	41/23,31	H = 21, L = 16
Cortisone therapy from 3/10/50 to 4/15/50	3/28/50	36	6	10	185	170	4.75	4.68	39/17,27	40/23,31	H = 21, L = 16
III, G.M. (Undiagnosed pulmonary disease)	5/12/50	51	53	3	149	183	3.55	5.56	48/20,31	49/18,30	H = 30, L = 25
ACTH therapy from 5/22/50 to 6/6/50	6/ 5/50	42	13	5	123	127	2.79	3.10	27/11,18	35/18,25	H = 21, L = 18.5

* Abbreviations: P.D.S., physiologic dead space expressed as per cent of tidal air; V.A., physiologic venous admixture expressed as per cent of total pulmonary blood flow; oxygen cons., oxygen consumption; sq.m.b.s., square meter of body surface area; H, inspired air contains high percentage of oxygen; L, inspired air contains low percentage of oxygen; s/d,m., Systolic/diastolic, mean.

† Expressed as cc. of oxygen per minute per mm. Hg mean pressure gradient.

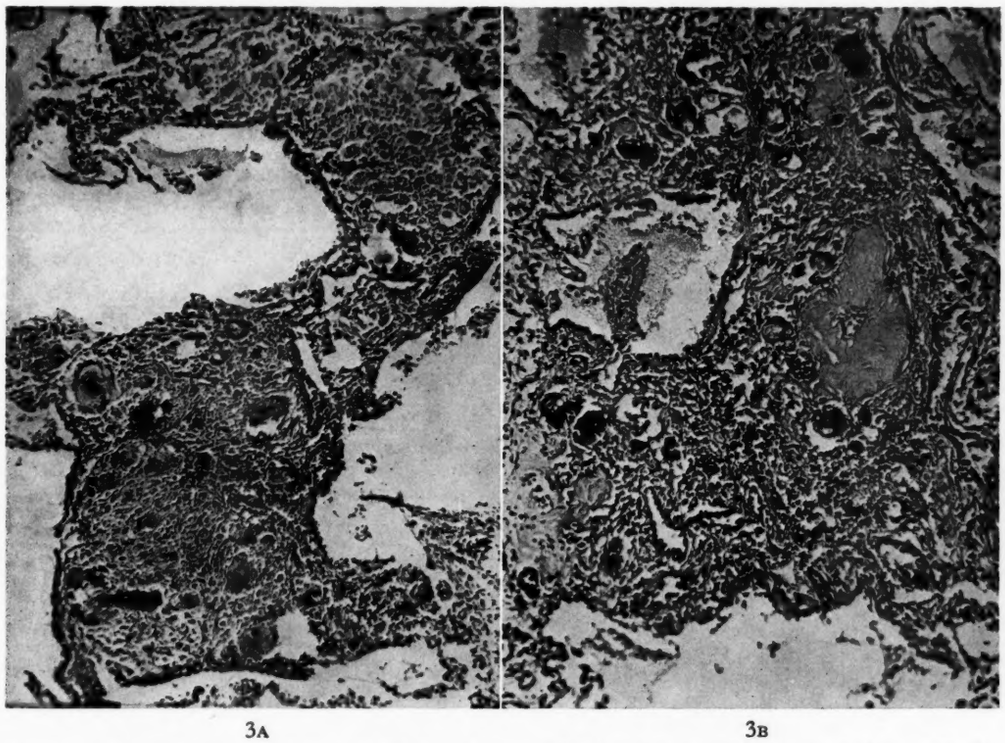
On April 13, 1950, the right chest was again explored. No enlarged lymph nodes could be found. The middle lobe seemed less granular than at the previous exploration, and a biopsy was taken from its anteromedial edge. On histologic examination the interstitial tissue of the lung was seen to contain numerous collections of doubly refractile material which was like that seen in the original lung biopsy. This material was still surrounded by numerous giant cells but the epithelioid cells seen in the previous sections were no longer present, having been replaced by a relatively acellular hyaline, collagen-like material which was fibrillar and pink-staining with hematoxylin-eosin stain and stained green with trichrome stain. (Fig. 3B.) Following cessation of treatment the patient was discharged from the hospital to be followed up in the clinic. The clinical improvements noted with cortisone therapy had not regressed two months after completion of the course of treatment.

CASE III. G. M., a twenty-six year old white housewife, was admitted to the Presbyterian Hospital on April 21, 1950, complaining of intense dyspnea, cyanosis, cough and a 20-pound weight loss of seven months' duration. She had been in good health until two years before admission when she noted the onset of mild exertional dyspnea. This slowly increased



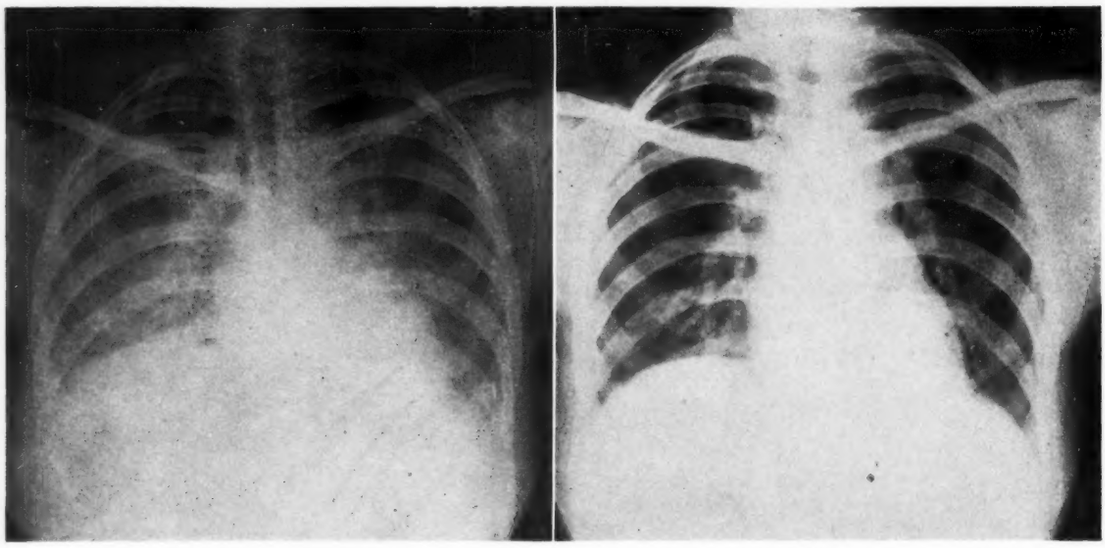
2A 2B

FIG. 2. A, x-ray of the chest of E. H., Case II, with pulmonary granulomatosis of unknown etiology before treatment with cortisone; B, x-ray of chest of same patient after treatment with cortisone.



3A 3B

FIG. 3. A, photomicrograph (× 136) of biopsy from cardiophrenic edge of right middle lobe of E. H., Case II, with pulmonary granulomatosis of unknown etiology before treatment with cortisone, showing pulmonary parenchyma infiltrated by interstitial granulomas; B, photomicrograph (× 182) of biopsy from anteromedial edge of right middle lobe of same patient with pulmonary granulomatosis of unknown etiology after treatment with cortisone, showing pulmonary tissue in which epithelioid cells have been replaced by hyaline-like material.



4A 4B

FIG. 4. A, x-ray of the chest of patient G. M., Case III, with pulmonary insufficiency of unknown etiology before treatment with ACTH; B, chest x-ray of same patient after treatment with ACTH.

in severity until approximately seven months before admission when following an upper respiratory tract infection dyspnea rapidly became more severe and soon was present at rest. Concomitantly the patient noted cyanosis of the nailbeds and lips after exertion, excessive fatigue and a dry hacking cough. These symptoms became so severe that the patient was forced to remain at bed rest for a month prior to admission. During this period of bed rest her temperature had ranged from 100° to 101°F.

There had been no chest pain, orthopnea, edema or hemoptysis. There had been no known exposure to tuberculosis, to other chronic infectious diseases of the lungs or to toxic fumes or dusts.

On admission to the hospital the patient's temperature (rectal) was 99.2°F.; the heart rate was 120 per minute, respiratory rate 40 per minute and blood pressure 83/50. The patient was emaciated, dyspneic, cyanotic and obviously in acute distress. The nails showed pronounced clubbing. Occasional fine rales were heard at both lung bases. The heart was somewhat enlarged, the apex being 1 cm. outside the midclavicular line. Its rhythm was regular. The pulmonic second sound was loud, snapping and greater than the aortic second sound. There was a systolic gallop rhythm. A very soft systolic murmur was heard in the pulmonic area. The remainder of the physical examination was not abnormal.

Pertinent laboratory findings included a white blood cell count of 13,000 per cu. mm. with a normal differential. Hemoglobin was 20.6 gm./100 cc. (Sahli), red blood cell count was 6.2 million per cu. mm. and the hematocrit was 53 per cent. Erythrocyte sedimentation rate (Westergren) was 8 mm./hr. Numerous blood cultures were negative. No sputum was available for examination. The Mazzini test was negative.

Chest x-rays and fluoroscopy revealed the heart to be moderately enlarged with prominence of the pulmonary vessels. The lung fields had a granular appearance. (Fig. 4A.) A skeletal survey was normal. The electrocardiogram revealed normal sinus rhythm, right deviation of the electrical axis and incomplete right bundle branch block.

The patient was afebrile throughout her course in the hospital except for two transient rises to 101°F. She was placed in an oxygen tent immediately after admission and in this high oxygen atmosphere (approximately 55 per cent) cyanosis and dyspnea were absent although tachypnea continued. After a few days in the tent it was found that the patient could not be removed for more than a few minutes without developing signs of approaching asphyxia. Ten days after admission the hematocrit was 41.5 per cent and the heart size had returned to normal, but the appearance of the lung fields had not changed.

On May 12, 1950, twenty-one days after

admission, the first detailed physiologic study was performed. (Tables I and II.) Beginning May 22, 1950, adrenocorticotropic hormone (ACTH),* 25 mg. intramuscularly every six hours, was given. After three days the dose was reduced to 12.5 mg. every six hours and was continued at this level for eleven more days.

A dramatic clinical improvement was noted with ACTH therapy. (Fig. 5.) After three days of treatment the patient no longer required oxygen therapy. After two weeks the only obvious evidence of pulmonary insufficiency at rest was a moderate degree of tachypnea. The lungs were clear to auscultation and x-ray of the chest revealed the lung parenchyma to be almost normal in appearance. (Fig. 4B.) The pulmonary vascular shadows, however, remained prominent. There was no change in hemoglobin. Except for a striking increase in voltage of the QRS complexes the electrocardiogram had not changed.

On June 6, 1950, after the second detailed physiologic study had been performed (Tables I and II), ACTH was replaced by saline injections. Within three days the patient complained of severe dyspnea and was slightly cyanotic. Consequently, on June 9th treatment with ACTH was reinstituted (25 mg. every six hours for five doses). Simultaneously cortisone acetate† therapy was begun, the dosage being 150 mg. on the first day, 350 mg. on the second, 200 mg. on the third, 100 mg. daily for three additional days and 100 mg. three times per week beginning June 16, 1950. On July 7, 1950, the dosage of cortisone was reduced to 50 mg. three times per week. Three days after the institution of cortisone therapy cyanosis and dyspnea had again disappeared and the patient has remained free of these symptoms since that time. At present she is at home, up and about, with no manifest evidence of pulmonary insufficiency. There has been no evidence of toxicity to either ACTH or cortisone other than slight fullness of the face.

COMMENTS

Before ACTH or cortisone therapy was started all three patients were shown to have reduction in the lung volumes with relative preservation of the maximum breathing capacity, hyperventilation at rest or on exercise and arterial oxygen unsaturation at rest or after exercise. (Table I.) In addition all were shown to have a reduction in the oxygen-diffusing capacity of the lungs, and in two of the three patients (E. H. and G. M.) there was a significant increase

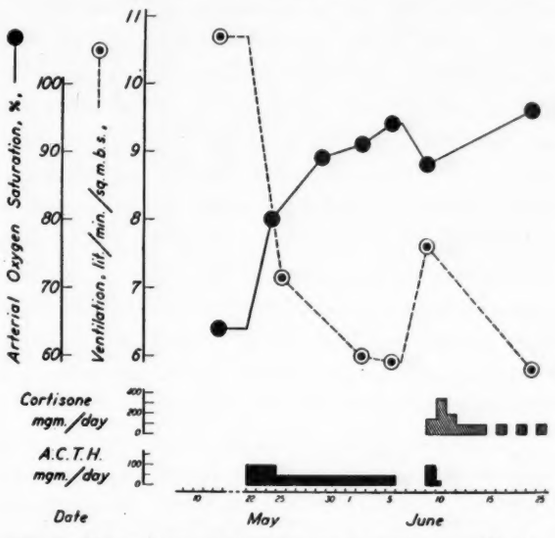


FIG. 5. Chart showing the changes in resting ventilation and arterial oxygen saturation in association with ACTH and cortisone therapy in a patient (G. M., Case III) with pulmonary insufficiency of unknown etiology. The measurements of May 12th were made while the patient was breathing air containing 25 per cent oxygen. Subsequent measurements were made while the patient was breathing air containing 21 per cent oxygen (room air).

in the physiologic dead space and in the physiologic venous admixture. These same two patients had pulmonary arterial hypertension at rest. (Table II.)

After therapy there was no significant change in the pattern of pulmonary dysfunction of the patient (M. M.) with pulmonary scleroderma. The other patients (E. H. and G. M.), on the other hand, demonstrated clinical improvement as well as betterment in some of the objective indices of pulmonary function. (Tables I and II.) There was no change in the lung volumes or maximum breathing capacity in one (E. H.), but there was a reduction in the degree of hyperventilation observed at rest and after exercise and a reduction in the degree of arterial unsaturation following exercise. (Table I.) In this patient there was only a slight reduction in the size of the

* Armour and Company, Chicago, Ill.

† Purchased from Merck and Company, Inc., Rahway, N. J. with funds provided by The United States Public Health Service.

physiologic dead space, a slight increase in the oxygen-diffusing capacity, but a definite reduction in the size of the physiologic venous admixture. Pulmonary arterial hypertension persisted. (Table II.) In the case of the third patient (G. M.) there was an improvement in vital capacity and maximum breathing capacity together with a reduction in resting ventilation and a striking increase in resting arterial oxygen saturation. (Table I, Fig. 5.) There was again a slight decrease in the physiologic dead space, a slight increase in the oxygen-diffusing capacity and a striking reduction in the size of the physiologic venous admixture. In addition there was a definite reduction in resting pulmonary arterial pressure with an elevation noted while breathing a low oxygen mixture. (Table II.)

Although the clinical diagnoses were varied, the fundamental basis of the pulmonary insufficiency observed in each of the three patients was shown to be the same, namely, an impairment of gas exchange between alveolar air and capillary blood. The nature of this impairment of gas exchange was further defined by the demonstration of a low oxygen-diffusing capacity in each instance indicating a defective alveolar-capillary membrane.

An increase in the number of inadequately ventilated although well perfused alveoli was suggested in two of the three patients (E. H. and G. M.) by the demonstration of a large physiologic venous admixture. An alternative explanation of such a finding is that certain portions of the alveolar-capillary membrane in these cases were so seriously deranged that oxygen diffusion was greatly impaired even in the presence of high partial pressures of oxygen in alveolar air. In such circumstances the grave impairment of diffusion, even in the absence of poorly ventilated alveoli, would be measured as an augmented physiologic venous admixture.

The abnormally large physiologic dead space that was observed in two of the three patients (E. H. and G. M.) prior to therapy suggested that there was an increase in the number of poorly perfused although well ventilated alveoli. Again, an alternative explanation of this finding lies in the concept that the reduction in or absence of gas exchange in these alveoli may be merely a reflection of extreme impairment of gaseous diffusion across the alveolar-capillary membrane and need not necessarily indicate a reduction in the actual amount of perfusion of these alveoli.

The major change observed in the two patients (E. H. and G. M.) who responded to treatment appeared to be a reduction in the size of the physiologic venous admixture, there being only a moderate increase in the oxygen-diffusing capacity. This reduction in the physiologic venous admixture could have resulted from: (1) an improved ventilation of certain inadequately ventilated alveoli, (2) the rerouting of blood from capillaries in poor contact with alveolar air to capillaries in better contact or (3) an improvement in the diffusion of oxygen in certain areas where diffusion had been so greatly impaired as to bring about an increase in the physiologic venous admixture. The latter mechanism would account also for the reduction in the physiologic dead space that was observed in these two patients after treatment although it is true that this improvement was small. The lung biopsies obtained in Case II do not contribute greatly to an understanding of this reduction in the physiologic venous admixture for although demonstrating profound changes in the lung following treatment they do not indicate the exact relationship of these changes to alveolar-capillary function.

Pulmonary arterial hypertension observed in Case I while on 14 and 16 per cent oxygen in the inspired air was probably a direct effect of anoxia.[11] That observed in Case II cannot be said to be due to anoxia; a reduction in the size of the pulmonary vascular bed is probably a more likely explanation. The pulmonary arterial hypertension observed in Case III prior to treatment and on 18.5 per cent oxygen in the inspired air after treatment was probably the result of anoxia also. This is supported by the fact

that there was no pulmonary hypertension on 21 per cent oxygen after treatment.

The different responses to treatment in Cases I and II can perhaps be explained by a consideration of the pathologic processes in the two cases. Although a biopsy of the lungs was not obtained in Case I, it is not unreasonable to assume that the pathology was like that seen in other cases of scleroderma.[1,12,13] The dense collagenous and hyaline material present in the alveolar septa in this disease might be expected not to respond to cortisone, in contrast to the granulomatous process in the lung of the patient in Case II. This contention is supported by the histologic appearance of the lung in Case II *after* treatment when it was seen that the epithelioid cells had been replaced by collagenous hyaline-like material.

In Case III since the etiology was unknown and no biopsy was performed, speculation regarding the anatomic changes effected by ACTH therapy cannot be supported by direct observations. It is attractive, however, to postulate the existence in the lungs before treatment of a highly vascular granulomatous process which resulted in impairment of gaseous diffusion across the alveolar-capillary membrane and which was reduced in its extent by hormonal therapy.

SUMMARY

A report is made of three patients in whom there was pulmonary fibrosis with evidence of impairment of gaseous diffusion across the alveolar-capillary membrane. In one case the process was due to scleroderma, in another it was secondary to pulmonary granulomatosis of undetermined etiology and in the third it was of unknown cause.

The clinical and physiologic effects of ACTH or cortisone in each patient are presented. The patient with scleroderma was not benefited by therapy. The other two patients were improved, at least temporarily, one strikingly so. Mechanisms of action of these hormones in these patients are discussed.

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Effect of ACTH in Chronic Lung Disease*

A Study of Five Patients

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THE effectiveness of adrenocorticotropic hormone (ACTH) in bringing about striking improvement in many instances of protracted asthma appears well established.[1] There have also appeared encouraging reports of its effectiveness in diseases of the lungs of such varied etiology as beryllosis,[2] lobar and primary atypical (viral) pneumonia,[3] Loeffler's syndrome[4] and of its ability to increase the tolerance of animals[5] and man[6] to anoxia. These reports have been documented by clinical findings and in some instances by pulmonary function studies limited to measurements of vital capacity, maximum breathing capacity and pattern of respiration.

It appeared important to find out whether ACTH might not also benefit patients suffering from such chronic lung diseases as pulmonary emphysema; chronic asthma complicated by pulmonary emphysema and fibrosis with and without cor pulmonale; pulmonary fibrosis, emphysema and bronchiectasis; and Boeck's sarcoid. It was believed that comprehensive evaluation of the disturbances of pulmonary function in a small group of such patients might help to establish the physiologic bases for the action of ACTH and possibly aid in the selection of patients for future investigation and therapy.

METHODS

Studies were carried out before, during and, whenever possible, following ACTH administration in five patients. Observations were also made during control periods when sterile water was injected intramuscularly in a dosage schedule similar to that used with ACTH. The patients were unaware of any difference in the nature of the injections. Frequent clinical, roentgenographic and electrocardiographic examinations were made.

The methods employed in the pulmonary function tests, their theoretic bases and clinical application have recently been admirably described[7–14] and therefore will not be detailed. They permit measurement of the total lung volume and a comprehensive evaluation of the proportionate relationship of the component parts to the whole, of the static and dynamic aspects of pulmonary ventilation, efficacy of distribution of gas in the lungs, integration of the distribution of gas and blood to the alveoli and diffusing capacity of the alveoli for oxygen.

Certain modifications of some of these methods employed in our laboratory during the past several years should, however, be described. That part of the circuit used for the collection of alveolar air during the measurement of mid-capacity is dispensed with. Instead, an air sample is collected directly into a mercury gas sample tube, evacuated to about 15 to 20 cc., at the end of a normal expiration. The free end of the tube projects a few millimeters into the airway just distal to the lips through an air-tight opening in the rubber mouthpiece. The main valve to which the mouthpiece is attached is turned to a neutral position at the end of expiration immediately before the air sample is collected, thus insuring collection of an uncontaminated sample. The oxygen and carbon dioxide tension of such gas samples have been found to agree closely with those of end-expiratory Haldane-Priestley samples, with

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arterial blood, and with mean effective alveolar air in healthy subjects.[15]

In the method for direct determination of arterial blood oxygen and carbon dioxide tension[8] the gas bubbles used for equilibration with blood are drawn from commercially prepared gas tanks with oxygen tension within approximately 20 mm. Hg of that expected in the blood sample, instead of relying on the chance collection of a sample of alveolar air expelled by the analyst into a narrow-mouth rubber bag. When the size of the bubble is measured, the syringe is placed horizontally in a metal tray with a white background suspended about 1 inch below the upper surface of the water bath. The accuracy of the measurement is aided by bringing the upper end of the bubble to the one unit mark and by the use of a magnifying glass. The need for oxygen and carbon dioxide tension correction factors has not appeared necessary.[16]

Maximum breathing capacity tests were carried out in the usual manner generally two to three times a week, occasionally once. Three and occasionally four successive tests were performed and at least two always agreed closely. The average of the highest daily values for each week is given when the results of the tests carried out on different days agree within 10 per cent; otherwise highest daily values are listed for each week. When the results of the tests carried out over several weeks agreed within these limits, the average of the several weeks is given.

Vital capacity was measured in the erect position with the patient first in maximal expiration. Two, three and occasionally four tests were carried out at a time. The values listed were arrived at according to the same criteria as for the maximum breathing capacity tests.

Results of all ventilation and lung volume determinations are expressed at body temperature, ambient pressure, saturated.

The per cent venous admixture and diffusing capacity of the lungs for oxygen were calculated by means of integration charts kindly made available to us by Dr. Richard L. Riley and Dr. Andre Cournand. Data on arterial blood-mixed venous blood oxygen per cent saturation difference, mean effective alveolar air oxygen tension, arterial blood oxygen tension and rate of oxygen consumption per minute at two different levels of oxygenation serve as a basis for the calculations. In our studies all of the essential data were derived by actual measurements except for the arterial blood-mixed venous blood oxygen per cent saturation differences which were assumed to be 25 or 30 per cent depending upon the clinical condition of the patient. Measurements of arterial blood-mixed venous blood oxygen per cent saturation differences in patients similar to those we studied indicate that the values assumed are likely close to the true values. In the range of arterial blood-venous blood oxygen per cent saturation differences employed, moderate deviations from the true values introduce only relatively small differences in the final results.

Observations of the effect of ACTH on certain blood constituents were also carried out. Plasma sodium and potassium were measured in an internal standard flamephotometer;[17] chloride according to Wilson and Ball;[18] carbon dioxide content by the method of Van Slyke and Neill,[19] pH in a Beckman sealed glass microelectrode accurate to ± 0.01 pH units and in most instances calculated by means of the nomogram of Van Slyke and Sendroy.[20] The blood eosinophile level was counted by the method of Randolph.[21] Total and differential white blood cell and red blood cell counts, hemoglobin (Sahli) and hematocrit measurements were also carried out. Tests of fasting blood sugar, oral glucose tolerance and in some instances liver function tests were also made.

CASE 1. *Diagnosis: bronchial asthma, pulmonary emphysema and fibrosis.*

W. H., a fifty year old white male, was admitted to the Goldwater Memorial Hospital on June 1, 1948, because of severe asthma. He had worked in stone quarries from the age of ten to thirty when he stopped because of the onset of asthmatic attacks. Since then asthma recurred during almost every summer and often followed pulmonary infection. He had suffered intermittently from postprandial epigastric distress since the age of forty-six (1946).

On admission the patient appeared well developed and fairly well nourished. Respirations were rapid, shallow, with retraction of the interspaces, and involved the accessory muscles of respiration. There was moderate increase in the anteroposterior diameter of the chest, and kyphosis of the dorsal spine. The trachea was deviated slightly to the right. The lung fields were hyper-resonant throughout, expiration was prolonged, breath sounds were diminished and there were numerous sibilant and sonorous rales in both phases of respiration. There was faint

cyanosis of the lips and nail beds but no clubbing of the fingers. The heart sounds were not audible, pulse was regular, 120 per minute, and arterial blood pressure 120/80. The liver and spleen were not palpable. There was no edema.

On roentgenographic examination there was emphysema with bleb formation in the upper lobes of the lungs, fibrosis in the lower lobes, deviation of the trachea to the right. The configuration of the heart and aorta was normal. The diaphragm moved only 1.5 cm. between maximum inspiration and expiration. There was clouding of the right maxillary sinus. Spasm of the prepyloric and duodenal regions was noted in a gastrointestinal series. An electrocardiogram exhibited peaked P waves in Leads II and III, sinus tachycardia, no deviation of the electrical axis. There were 4.4 million red and 10,000 white blood cells per cu. mm. with a normal differential white blood cell count, and 15 gm. hemoglobin. Urine examination showed no abnormalities.

During the period of nearly two years that the patient was observed in the hospital prior to the administration of ACTH, he was incapacitated most of the time by asthmatic attacks. There were numerous brief febrile episodes accompanied by cough and chest pain but only occasionally by new physical and roentgenographic findings of bronchopneumonia. These responded to penicillin. Greatest relief from acute asthmatic attacks was attained from the use of oxygen and vaponefrin inhalations and aminophylline intravenously. However, no combination of medicines appeared to prevent these attacks. He occasionally expectorated small amounts of non-foul sputum which did not contain pathogenic organisms. Epigastric pain occurred intermittently and was relieved by dietary control, antacid and antispasmodic medications. His weight gradually fell from 145 to 117 pounds. There was no other significant change in physical findings. There was no melena and urine examination showed no abnormalities. Other laboratory studies carried out shortly before the start of ACTH administration are summarized in Table I.

The patient received 10 mg. ACTH intramuscularly four times a day for thirty-six days, from May 16th through June 21st. On the second day there was dramatic improvement in mood, considerable relief from respiratory distress and decrease in prolongation of expiration and number of adventitious lung sounds. Asthmatic attacks did not occur throughout the period of ACTH administration. Appetite increased strikingly. He voluntarily stopped taking all bronchodilator medications and inhalations of oxygen. The level of arterial blood pressure remained unchanged and the heart rate gradually decreased to between 90 and 100 per minute. Acne appeared on the shoulders, chest and arms by the ninth day and persisted well beyond cessation of ACTH administration. There was a gradual gain of 15 pounds in weight, from 117 to 132 pounds, unassociated with clinical signs of fluid retention. There was no change in ulcer symptoms. The results of hematologic and metabolic studies carried out during the period of ACTH administration are summarized in Table I. Weekly electrocardiograms and teleroentgenograms exhibited no changes.

By the end of the second week after discontinuance of ACTH the patient had gradually regressed to his previous incapacitated asthmatic state. On July 7th, two weeks after ACTH had been stopped, injections of 1 cc. sterile water four times a day were begun and continued for one week. The patient did not exhibit any improvement. His appetite remained poor but he did not lose weight. Previously noted acne had almost completely receded. The patient was concerned over the failure of the injections to relieve him this time. He was encouraged to be patient and advised that in time we hoped to be able to attain again a proper dosage for him. The eosinophile and hematologic data obtained during this period are listed in Table I.

On July 14th intramuscular injections of 10 mg. ACTH four times a day in 1 cc. sterile water were substituted for the sterile water. In general the patient exhibited as striking a response as previously. Body weight rose from 130 to 144 pounds. Acne of the arms, shoulders and chest reappeared but was not troublesome. This time the eosinophile level did not exhibit a consistent depression and the plasma electrolyte levels exhibited changes similar to those noted during the previous period of ACTH administration. (Table I.)

Pulmonary Function Studies (Tables II and III): Prior to administration of ACTH the vital capacity was greatly reduced, total lung capacity moderately increased, ratio of residual air to total capacity markedly increased, maximum breathing capacity considerably reduced and distribution of gas in the lungs impaired. There was poor integration of gas and blood distribu-

TABLE I

Patient	Period	Day of Period	Body Weight (lb.)	Arterial Blood Pressure (mm. Hg)	Hematocrit (%)	Eosinophiles (no./cu.mm. blood)	Plasma Sodium (mEq./L.)	Plasma Potassium (mEq./L.)	Plasma Chloride (mEq./L.)	Plasma Carbon Dioxide (mEq./L.)	Whole Blood pH	Glucose Tolerance Curve
W. H.	Control	1	117	120/80	45.0	...	143.2	3.8	98.4	27.9	7.42	.....
		11	117	130/86	48.5	492	137.4	4.3	93.0	33.0	7.44	Normal
	ACTH 10 mg. 4 i.d.	8	119	140/80	41.0	100	131.4	3.6	102.5	27.4	7.46	.....
		16	123	118/80	42.0	100	133.6	3.4	101.2	27.5	7.50	Normal
	Sterile water 1 ml. 4 i.d.	7	130	130/80	52.0	964	135.6	4.5	93.0	38.3	7.37	.....
	ACTH* 10 mg. 4 i.d.	26	139	120/70	44.0	350	129.0	3.4	103.0	28.3	7.49	.....
H. R.	Control	3	152	140/80	54.0	198	138.6	4.6	95.6	38.9	7.40	Normal
	ACTH 20 mg. 4 i.d.	18	155	160/100	50.0	11	137.2	3.9	100.2	45.0	7.46	Diabetic
	Sterile water 1 ml. 4 i.d.	18	162	128/80	....	173	140.0	5.7	92.1	39.0	....	Diabetic
	ACTH 5 mg. 4 i.d.	5	164	150/90	....	159	138.4	6.4	102.6	30.6	....	.....
	ACTH 10 mg. 4 i.d.	3	169	160/90	....	63	140.0	4.8	95.0	35.3	....	Normal
		10	162	170/110	....	98	137.4	5.4	95.7	....	....	.....
	Control	5	166	118/90	....	59	135.0	5.9	92.4	34.2	....	.....
		29	167	140/100	54.0	...	131.0	4.3	97.7	38.5	7.38	Normal
I. R.	Control	3	117	110/70	38.0	133	137.8	4.6	107.5	24.2	7.40	Normal
		8	119	116/74	....	120	134.4	5.4	108.5	....	....	.....
	ACTH 10 mg. 4 i.d.	9	118	108/78	....	0	134.2	4.4	104.0	28.8	....	Diabetic
		15	128	130/78	27.5	0	137.2	4.7	105.2	26.9	7.47	.....
		19	122	128/74	....	0	.....	...	101.0	31.5	....	Diabetic
D. T.	Sterile water 1 ml. 4 i.d.	8	145	140/85	48.0	221	131.4	4.6	94.6	28.2	7.46	Normal
	ACTH 10 mg. 4 i.d.	9	147	130/80	45.0	92	133.6	4.3	98.5	29.2	7.50	Diabetic
		16	149	150/80	....	102	136.0	4.1	100.2	29.0	....	Diabetic
	ACTH 15 mg. 4 i.d.	5	150	132/86	....	116	133.4	4.8	104.6	28.3	....	.....
	ACTH 20 mg. 4 i.d.	3	152	136/90	....	31	140.0	4.2	99.5	30.8	....	Diabetic
		10	149	130/80	....	96	136.0	4.5	97.0	31.7	....	.....
	Control	5	144	118/82	....	36	131.2	4.8	97.5	27.8	....	.....
		29	146	130/80	43.0	...	123.6	4.1	111.0	28.0	7.41	Normal
E. C.	Sterile water 1 ml. 4 i.d.	1	96	170/80	50.0	64	131.4	4.7	94.5	31.3	7.40	.....
	ACTH 10 mg. 4 i.d.	3	96	172/82	....	25	145.4	3.8	111.5	28.3	....	.....
	Control	4	96	.....	....	48	137.4	4.3	98.1	....	....	.....

* This dosage was continued for 5 weeks during which time his clinical improvement was sustained. The dose was then reduced to 6.25 mg. 4 i.d. and he exhibited no regression.

TABLE II

Patient, Age, Sex, Diagnosis	Period	Date 1950	Vital Capacity (ml.)	Total Capacity (ml.)	Residual Air Total Capacity (%)	Index Intra-pulmonary Mixing ($\%N_2$)	Ventilation (L./min./M^2)	Arterial pO_2 (mm. Hg)	Alveolar pCO_2 (mm. Hg)	Dead Space, Tidal Air (%)	Venous Admixture (%)	Oxygen Diffusing Capacity (ml./min./mm. Hg)
			(3580)*	(5170)*	(31)*	(2.5 or less)†	(3.2–4.9)†	(90–100)	(36–42)	(30 or less)‡	(7 or less)§	(15 or more)§
W. H. 50 M	Control	4/24					8.3	58	43	59	25	10**
		4/24–5/21	5/2	2110	5400	61	3.8	6.8	62	50	57	19	10**
Bronchial asthma; pulmonary emphysema; fibrosis	ACTH 10 mg. 4 i.d. 5/16–6/21	5/22	2710	5300	49	2.5	7.0	77	38	47	15	14
		6/12	3380	5910	43	2.0	6.9	93	35	43	7	13
	Sterile water 1 ml. 4 i.d. 7/7–7/13	7/12	1360	5520	75	4.2	7.4	48	67	56	30	15**
	ACTH 10 mg. 4 i.d. 7/14–9/29	8/7	3270	5450	40	1.5	6.1	90	39	44	10	11
			(3940)*	(5700)*	(31)*		(3.2–4.9)†					
H. R. 50 M	Control 3/21–4/23	3/21	1220	4230	71	5.0	4.9	44	67	52	35	14
							5.2	49	58	52	..	..
Bronchial asthma; pulmonary fibrosis; emphysema; cor pulmonale	ACTH†† 20 mg. 4 i.d. 4/24–5/15 10 mg. 4 i.d. 5/16–5/23	5/3	1650	4180	61	4.6	4.5	41	74	53	32	16**
		7/11	1430	5440	74	3.2	...	..	..	..	..	..
	Control 7/13–8/10	7/25	2270	5660	60	2.5	5.2	45	69	61	16	22
		8/9	1710	4620	63	3.1	...	..	..	..	..	..
			(3130)*	(3920)*	(20)*		(2.5–4.3)†					
I. R. 22 F	Control 3/27–4/4	3/30	2030	2470	18	1.5	5.9	86	40	40	7	17
Boeck's sarcoid	ACTH 10 mg. 4 i.d. 4/5–4/27	4/14	2310	3100	25	1.6	5.3	88	37	25	less than 7	more than 15
			(3520)*	(5090)*	(31)*		(3.2–4.9)†					
D. T. 64 M	Control 5/12–5/22	5/12	2020	4160	51	2.7	5.8	80	40	51	10	14
Bilateral apical and subapical pulmonary fibrosis and bronchiectasis secondary to inactive tuberculosis; emphysema	ACTH‡‡ 10 mg. 4 i.d. 5/23–6/20	6/15	2180	5330	59	2.4	4.9	78	39	43	13	15
	Control 7/13–8/15	7/24	2420	4790	50	2.3	5.3	84	46	55	less than 7	more than 15
		8/15	2220	4270	48	2.2	...	..	..	..	..	..
			(3270)*	(4720)*	(31)*		(3.2–4.9)†					
							5.1	72	42	48	14	7
E. C. 74 M	Control	9/30/49	1880	5040	63	8.1	4.9	71	45	50	..	..
Pulmonary emphysema	ACTH 10 mg. 4 i.d. 7/1–7/7	6/30	1430	4970	71	6.5	5.0	58	50	55	28	8
		7/1–7/7	Observations could not be obtained									

* Predicted value.[7]
† Normal range.[7]
‡ Normal range.[11]
§ Normal range.[14]
** Per cent venous admixture and oxygen diffusing capacity calculated assuming an arteriovenous oxygen per cent saturation difference of 30 per cent. All other calculations were made assuming a 25 per cent arteriovenous oxygen saturation difference.
†† Subsequent injection schedules were: 6/3–6/20 1 cc. sterile water 4 i.d.; 6/21–7/12 ACTH 5 mg. 4 i.d.
‡‡ Subsequent doses of ACTH were: 6/21 15 mg. 4 i.d.; 7/1–7/6 20 mg. 4 i.d.; 7/7–7/12 10 mg. 4 i.d.

tion to the alveoli resulting in a large component of venous admixture and the alveolar diffusing capacity for oxygen was moderately reduced. The graphic respiratory records obtained during the vital capacity and maximum breathing capacity tests revealed a striking degree of obstruction to expiration. These findings indicate the presence of advanced pulmonary emphysema characterized by ventilatory, alveolar oxygen diffusion, and alveolar gas and blood distribution deficiencies.

The studies carried out while the patient received ACTH indicate a striking improvement in all of the measured pulmonary functions. The vital capacity was normal, the ratio of residual air to total capacity decreased, leaving only a moderate degree of pulmonary distention; maximum breathing capacity gradually more than doubled to reach just below the lower limit of the predicted level; intrapulmonary mixing of gas was normal but the dead space/tidal air ratio though considerably smaller was still moderately increased. The integration of gas and blood distribution to the alveoli was now good so that the venous admixture component was within the normal range. Oxygen diffusing capacity was normal.

Following cessation of ACTH administration there was gradual deterioration in pulmonary function. When distilled water was administered in a manner similar to ACTH, there was no subjective or objective improvement. By the time ACTH injections were resumed almost one month after they had been stopped, the pulmonary function studies indicated regression to the severely handicapped pre-treatment state. ACTH was as effective as previously in relieving the patient's pulmonary impediments.

CASE II. *Diagnosis: bronchial asthma, pulmonary fibrosis, emphysema and cor pulmonale.*

H. R., a fifty year old white male, was transferred from another hospital to Goldwater Memorial Hospital on February 4, 1950, with a diagnosis of bronchial asthma, pulmonary fibrosis and emphysema, and cor pulmonale. In October, 1949, and again in January, 1950, he had been admitted to the hospital with signs and symptoms of congestive heart failure, predominantly right-sided. On both occasions he improved on bed-rest and intramuscular injections of adrenaline in oil.

Since the age of five he had suffered from repeated asthmatic attacks and had often required hospitalization for relief from them. There was no history of allergy, seasonal occurrence or familial incidence of asthma.

On admission to Goldwater Memorial Hospital he appeared chronically ill but fairly well nourished, with a cyanotic tint to the skin, lips and nail beds. Respirations were rapid, shallow and involved the use of accessory muscles of respiration. There was marked retraction of the lower one-third of the chest on inspiration. The anteroposterior diameter of the chest was increased and there was pigeon-breast deformity of the sternum which was more marked on the right half. The lung fields were hyper-resonant at the bases and in the axillas. The breath sounds were distant except at the apices and there were numerous sibilant and sonorous rales throughout and occasional medium moist inspiratory rales over the bases and axillas. The heart was enlarged to the left; P_2 equalled A_2; rhythm regu-

TABLE III
CASE I

Period	Week	Maximum Breathing Capacity (L./min.)	Vital Capacity (ml.)
		(97.4)*	(3,580)†
Control	1	21.0	1,660
ACTH	2	28.1	2,380
		31.7	
	3–4‡	54.2	3,460
	5	44.1	2,520
	6	75.6	3,420
		62.0	
Control	7	50.7	3,070
			3,500
	8	26.8	1,980
Water	9	27.0	2,040
ACTH	10	21.9	1,830
		32.6	2,100
			2,720
	11	47.9	3,380
		40.6	
	12	61.5	3,560
		45.8	3,120
	13	39.8	2,710
		53.0	3,640
		67.8	
	14	52.0	3,460
		60.0	
	15	47.1	3,300
	16	54.5	3,330

* Predicted value.[7]

† Predicted value for recumbent position.[7] Observations were made in erect position in which predicted values are probably 5 to 10 per cent higher.

‡ Inclusive.

lar, 90 per minute. There was a short apical systolic murmur. Arterial blood pressure was 130/80. The liver and spleen were not felt. There was no clubbing, ankle or presacral edema.

X-ray examination revealed pulmonary emphysema, fibrosis of the apices and mild congestion of the lungs with generalized cardiac enlargement. Moderate clouding of the left antrum was evident. There was electrocardiographic evidence of right ventricular hypertrophy and sinus tachycardia. The level of venous pressure in the antecubital vein was 70 mm. of water. It did not rise on abdominal pressure nor after one minute of exercise. Circulation time measured with ether and decholin was normal. There were 6.1 million red blood cells per cu.mm. of blood and 17 gm. of hemoglobin per 100 cc. of blood. The total white blood cell count was 9,000 per cu.mm. of blood and the differential count was normal. The urine examination revealed no abnormalities.

During the three-month period of observation in the hospital prior to receiving ACTH asthmatic attacks occurred almost daily and sometimes several times a day. These were relieved by subcutaneous injection of ½ cc. of adrenalin. Between attacks the patient received aminophylline suppositories twice daily and ephedrine sulfate 0.025 gm. periodically. His physical activity was moderately limited by shortness of breath and he had orthopnea. There was little evidence of cardiac failure. His weight varied between 150 and 155 pounds. He expectorated only small amounts of mucoid, non-foul sputum which did not contain pathogenic organisms.

Six days prior to the administration of ACTH, all medications, except adrenalin as necessary, were discontinued in order to observe the frequency of acute asthmatic attacks. He was also placed on a salt-poor, acid-ash diet. This did not result in any weight loss. The metabolic and hematologic data collected at this time are presented in Table 1. There was no demonstrable abnormality of liver function. Occult blood was not noted in the stool.

Twenty mg. of ACTH four times a day were administered intramuscularly during the three-week period from April 24th through May 15th. From the second through the fourth day there appeared to be moderate relief from respiratory distress. Toward the end of the first week asthmatic attacks recurred and from then on the patient required at least one injection of adrenalin daily. On the sixth day of therapy there was a trace of pretibial edema which increased to one plus on the tenth day when moon facies also became evident. There was a gain of 7 pounds (from 155 to 162 pounds) during the first week with daily fluctuations of as much as 4 pounds. From then on there was no further weight gain. Starting with the third day the arterial pressure began to rise from a normotensive level to 170/110 on the seventh day. Thereafter it varied between 140–190/90–110 until ACTH discontinuance. Acne of the chest, shoulders and arms was evident toward the end of the third week. Fluoroscopic and teleroentgenographic examination on the twenty-first day showed further increase in the degree of cardiac enlargement. There was no change in the appearance of the lung fields in teleroentgenograms and in the electrocardiographic pattern repeated at weekly intervals. Venous pressure in the antecubital vein was now 135 mm. of water and it rose to 150 mm. on abdominal pressure and 190 mm. after one minute of exercise. Ether and decholin circulation times remained normal.

Because of the evident increasing congestive failure the dose of ACTH was cut to 10 mg. four times a day at the start of the fourth week and continued for seven days (from May 16th through May 22nd). During this time there was a gradual loss of the weight gained on the higher ACTH dosage. However, asthmatic attacks occurred with greater frequency.

The results of the hematologic and metabolic blood studies during these two periods of ACTH administration are summarized in Table 1.

Following discontinuance of ACTH the arterial blood pressure promptly fell to its previous level of 114–140/80–86. By the third day the patient reported that breathing required less effort. Asthmatic attacks continued to occur once or twice daily. There was no loss of weight and lung findings were unchanged. By the sixth day the moon facies was gone, and by the eighth day the previously noted acne was subsiding and the left ventricle appeared smaller on fluoroscopy.

Ten days after ACTH was stopped intramuscular injections of 1 cc. sterile water four times a day were begun and continued for the next eighteen days (June 3rd through June 20th). Although the patient reported that he felt better, he noticeably limited his physical activity more than ever and there were no

objective signs of improvement. His appetite improved when a regular salt-poor diet was substituted for the salt-poor acid-ash diet which he did not relish. His weight rose from 155 pounds to 162 pounds. There was no manifest edema. Arterial blood pressure remained at a normotensive level and the acne continued to recede. He still exhibited a diabetic type of tolerance curve but no glycosuria. The results of metabolic and hematologic studies at this time are shown in Table I.

After this prolonged control period it was decided to note the effect of a smaller dose of ACTH than had previously been given. On June 21st injections of 5 mg. ACTH four times a day were substituted for the sterile water injections. These were continued for the next ten days (through June 30th). There was no subjective or objective improvement, no significant change in weight, nor did signs of congestive failure appear.

The dose of ACTH was again increased to 10 mg. four times a day on July 1st and continued through July 12th. There was a gradual gain of 5 pounds (from 164 to 169) during the first nine days, followed by a spontaneous diuresis of 7 pounds on the tenth day, and a gain of 4 pounds during the next day. The weight gain was maintained on the twelfth and last day of ACTH administration. A smaller degree of heart failure and arterial hypertension developed on this dose than with the 80 mg. daily dose. There was no edema. This time the patient did not exhibit acne and moon facies. The blood eosinophile and plasma electrolyte levels for this period are presented in Table I.

Following discontinuance of ACTH the patient experienced somewhat less respiratory distress. Arterial blood pressure again returned to a normotensive level. Body weight continued to increase due to a large appetite and limited physical capacity. Plasma electrolyte levels except sodium remained unchanged. (Table I.)

Pulmonary Function Studies (Tables II and IV): The studies carried out before ACTH was administered showed a greatly diminished vital capacity, limited total lung capacity, with a strikingly increased residual air-total capacity ratio, markedly limited maximum breathing capacity, defective intrapulmonary distribution of gas, many poorly ventilated but well circulated alveoli resulting in a large venous admixture component and a normal alveolar diffusing capacity for oxygen. Graphic records of the respiratory pattern during the vital capacity and maximum breathing capacity tests showed considerable obstruction to expiration. These studies indicate marked ventilatory and alveolar-respiratory insufficiency compatible with advanced emphysema and fibrosis.

TABLE IV
CASE II

Period	Week	Maximum Breathing Capacity (L./min.)	Vital Capacity (ml.)
		(114.8)*	(3,940)†
Control	1	27.3	1,510
ACTH	2	37.7	1,930
		32.4	2,050
		17.5	‡
	3	22.5	1,470
			1,680
	4	26.2	1,900
		20.8	1,590
	5	20.9	1,410
Water	6	20.9	1,860
	7	19.8	1,860
		24.9	
	8	28.4	2,030
		17.9	1,350
ACTH	9	20.9	1,600
	10	20.8	1,580
		23.8	1,270
Control	11		
	12	29.1	1,950
	13	37.5	2,170
		27.1	1,860
	14	28.2	1,660

* Predicted value.[7]

† Predicted value for recumbent position.[7] Observations were made in erect position where predicted values are probably 5 to 10 per cent higher.

‡ Patient too short of breath to carry out this test.

There was no sustained salutary change in pulmonary function which could with certainty be ascribed to the administration of ACTH. The manifest variations in maximum breathing capacity and vital capacity during the periods when ACTH was administered and during the control periods are compatible with minor fluctuations in the severity of the asthmatic state.

CASE III. *Diagnosis: Boeck's sarcoid.*

I. R., a twenty-two year old negro housewife, was admitted to the hospital on July 5, 1949, complaining of migratory polyarthritis, cutaneous nodules on her legs, weakness and fever up to 101°F., all of about ten days' duration. There

was no history of any serious past illness. A teleroentgenogram exhibited normal cardiac contour and enlarged hilar lymph nodes. The erythrocytic sedimentation rate was 32 mm. per hour, antistreptolysin titer 1:142 and tuberculin test negative to 1:100 dilution. Aspirin gave relief from the joint pains. The nodules gradually disappeared. The patient was discharged after thirty-three days of hospitalization with a diagnosis of possible rheumatic fever and erythema nodosum, and instructed to attend the outpatient clinic. She continued to experience malaise, ease of fatigue and afternoon and night sweats. A Kveim test was performed and biopsy of the resulting lesion was reported positive for Boeck's sarcoid. Toward the end of September anorexia and a cough productive of yellow-white tenacious sputum developed. It was believed that the cough was due to bronchial irritation from the enlarged hilar lymph nodes. Cough was considerably relieved following radiation therapy, 600 r directed toward the nodes during the first week of October.

She was readmitted to the same hospital on October 11, 1949, because of the onset of frontal headache, dizzy spells, nausea, vomiting and shaking chills. A large, firm supraclavicular node was noted for the first time. There was dullness, diminished resonance and breath sounds at the bases of the lungs. There were no abnormal heart or joint findings. Hilar and mediastinal nodes were enlarged on roentgenograms. The tuberculin test was still negative in a 1:100 dilution. There were 3.1 gm. per cent of serum albumin and 3 gm. per cent of serum globulin. Because it was thought that the patient might have miliary tuberculosis, streptomycin and p-aminosalicylic acid were administered for six weeks, without improvement. The patient had lost 30 pounds in body weight since the onset of her illness.

She was transferred to Goldwater Memorial Hospital on November 30, 1949. Pertinent physical findings on admission at that time were: fever of 101°F., pulse 108 and respirations 24 per minute; arterial blood pressure 90/60; increased warmth and pain on movement of the right wrist; heat, fluid and tenderness in both knee joints; a gray, raised, crusted, non-tender Kveim test lesion, 1 cm. in diameter on the volar aspect of the right forearm; two similar lesions with clean ulcerated centers on the left arm; a palpable nodule at the angle of the left scapula and a few small discrete, freely movable axillary nodes; trachea midline; neck veins not distended; chest and lungs normal; second pulmonic sound louder than aortic second sound; liver edge smooth, non-tender, palpable 2.5 fingerbreadths below the right costal margin; no clubbing or edema.

The patient's course was marked by the following: fever ranging from 99° to 104°F., joint signs and symptoms waxed and waned, but there was some joint swelling or pain at all times. In the middle of February, 1950, papules measuring about 2 to 6 mm. in diameter appeared on the eyelids and anterior surface of the legs; there was exacerbation of joint pains; pea-size nodules could be felt in the subcutaneous tissue of the arms and abdomen; the tip of the spleen became palpable and two almond-sized lymph nodes developed in the left axilla. Treatment was entirely symptomatic.

Teleroentgenograms exhibited a normal configuration of the heart and aorta, enlarged right paratracheal and mediastinal lymph nodes. Roentgenograms of all bones and joints of the body appeared normal. Biopsy specimens of tonsillar tissue and Kveim test nodule of the forearm exhibited the characteristics of Boeck's sarcoid. Sinus tachycardia and right deviation of the electrical axis were present in the electrocardiograms. There were generally 4.6 million red blood cells per cu.mm., 12.5 gm. hemoglobin per 100 cc. blood, 6,000 white blood cells per cu.mm. and a normal differential count except for 9 to 16 per cent non-segmented cells. Examination of the bone marrow showed no abnormalities. The erythrocytic sedimentation rate varied from 20 to 50 mm. per hour; tuberculin test was negative to 1 mg.; gastric washings did not contain tubercle bacilli; blood trichinosis precipitin test was positive in 1:1280 dilution (had been negative in December, 1949); typhoid, paratyphoid, brucella and proteus OX19 blood agglutination tests were negative. Cephalin flocculation was 4+ at the end of twenty-four hours; thymol turbidity 10 units; acid and alkaline phosphatase and total cholesterol and cholesterol ester levels were normal. The hematologic and metabolic studies carried out shortly before the start of ACTH administration are summarized in Table 1.

All medications were discontinued when the patient was started on a regimen of 20 mg. of ACTH four times a day on April 5th and continued through April 27th. There was prompt clinical improvement. Joint pains and swellings

were completely gone in two to three days; appetite improved. The body temperature rose above 100°F. only four times in the twenty-three days and then no higher than 101.8°F., and the erythrocytic sedimentation rate fell from 50 mm. per hour to less than 20 mm. per hour. Kveim test lesions, skin papules and subcutaneous nodules gradually cleared. The large liver and spleen remained. Repeat roentgenograms of the chest showed the right paratracheal nodes to be slightly more pronounced than before. The patient's weight before therapy was 119 pounds and remained the same until the twelfth day when there was a sudden gain of 4 pounds. She maintained this weight until the eighteenth and nineteenth day when a loss of 5 pounds occurred. At that time she was in the second and third day of her menstrual period. On the tenth day of injection acne appeared on the face and chest and subsequently facial fullness and abdominal striae were noted. Early in the second week of therapy the patient exhibited beginning mental depression. This gradually became more intense despite improvement in symptoms. It was therefore thought best to discontinue the injections on the twenty-third day.

A tonsillar biopsy taken after twenty days of therapy showed regression of the sarcoid tissue by fibrosis and hyalinization. The results of the cephalin flocculation and thymol turbidity tests remained abnormal. The hematologic and metabolic studies carried out during the period of ACTH administration are summarized in Table I.

On the second day of ACTH discontinuance there was recurrence of joint pains, chill and fever up to 103°F. There was marked mental depression with paranoid tendencies. Dullness and diminished breath sounds were present at both bases. The fever and joint symptoms and abnormal lung findings continued on the third day when the patient jumped from an outside balcony and died a few hours later. Permission to perform an autopsy was not obtained.

Pulmonary Function Studies (Tables II and V): Studies carried out before ACTH was administered showed a decreased vital capacity and total capacity with a normal residual air-total capacity ratio, limited maximum breathing capacity, increased minute volume of respiration (the patient was afebrile at the time of these observations), defective distribution of gas in the lungs as indicated by a moderately increased dead space to tidal air ratio, normal relationship between alveolar ventilation and perfusion and normal alveolar diffusing capacity for oxygen. The respiratory pattern appeared normal during the vital capacity and maximum breathing capacity tests. The disturbances observed in this patient are consistent with early pulmonary fibrosis.

TABLE V
CASE III

Period	Week	Maximum Breathing Capacity (L./min.)	Vital Capacity (ml.)
		(108.1)*	(3,130)†
Control	1	70.3	2,030
ACTH	2	90.0	2,430
		102.5	
	3	94.5	2,400
		106.4	

* Predicted value.[7]

† Predicted value for recumbent position.[7] Observations were made in erect position where predicted values are probably 5 to 10 per cent higher.

During the period of ACTH administration the previously described deficiencies in pulmonary function were either partially or entirely corrected (Table II) except for a continued increased minute volume of respiration. It was impossible to repeat the pulmonary function studies following discontinuance of ACTH because of the patient's mental state.

CASE IV. *Diagnosis: bilateral apical and subapical pulmonary fibrosis and bronchiectasis secondary to old, inactive tuberculosis; pulmonary emphysema.*

D. T., a sixty-four year old white Italian male, a former gardner, entered a hospital early in 1933 complaining of recent onset of cough, expectoration and tightness in the chest. A diagnosis of active caseous pneumonic tuberculosis was made. He was discharged from the hospital in 1938 with a diagnosis of arrested, moderately advanced bilateral pulmonary tuberculosis and bronchiectasis. Symptoms continued as before and he was readmitted to the same hospital for observation many times during the next eleven years. He was transferred to the Goldwater Memorial Hospital for chronic care on January 9, 1950. He denied hemoptysis, orthopnea, dyspnea, night sweats or weight loss. There was no history of allergy or of exposure to dust and fumes. He underwent incision and

drainage of an abscess of the anterior aspect of the lower one-third of the right chest wall in 1912.

On admission to Goldwater Memorial Hospital he appeared well developed and well nourished. He weighed 145 pounds. There was no obvious respiratory distress, cyanosis, clubbing or edema. The trachea was in the midline. The anteroposterior diameter of the chest was slightly increased and there was a well healed scar over the anterior aspect of the lower one-third of the right half of the chest. Excursion of the chest was symmetrical and not limited. There were bronchial breath sounds, dullness and medium moist and consonating rales over the anterior and posterior aspects of the upper one-third of both lung fields. The heart was not enlarged; rhythm was regular. There was a soft apical systolic murmur and no thrills. The arterial blood pressure was 130/88. The liver edge which was palpable two fingerbreadths below the right costal margin was firm, smooth and non-tender.

A teleroentgenogram of the chest exhibited evidence of old bilateral apical and subapical tuberculosis with fibrosis and honeycombing, and emphysema elsewhere in the lungs. Configuration of the heart and aorta appeared normal. An electrocardiograph exhibited normal sinus rhythm and left deviation of the electrical axis.

There were 4.62 million red blood cells per cu.mm., with 15 gm. of hemoglobin per 100 cc. blood; white blood cells numbered 15,000 with a normal differential count. The erythrocytic sedimentation rate was 20 mm./hour and the hematocrit was 49 per cent. Smear and culture of the sputum did not reveal pathogenic organisms. Urine examination showed no abnormalities. The level of venous pressure in the antecubital vein measured 165 mm. water and did not rise on abdominal pressure. Ether and decholin circulation times were normal.

During the four months that the patient was observed in the hospital prior to the administration of ACTH he continued to cough and expectorate about 3 to 4 ounces of tenacious, mucoid, green, non-foul sputum a day. He complained chiefly of tightness and a sensation of oppression in the chest particularly when exposed to a draught. He was afebrile. There was no significant change in the clinical and laboratory findings. Treatment consisted of penicillin aerosol inhalations daily. The results of metabolic and hematologic studies carried out shortly before ACTH administration was begun are listed in Table I.

The patient received 1 cc. of sterile water intramuscularly four times daily during the four days prior to the start of ACTH administration. These were not accompanied by any clinical or laboratory changes. On May 23rd 10 mg. of ACTH were substituted for each sterile water injection and continued through June 20th without any beneficial effect. There was a similar lack of response when 15 mg. of ACTH were administered four times a day from June 21st through June 30th, and 20 mg. four times a day from July 1st through July 12th.

The metabolic, hematologic and clinical observations made during this prolonged period of ACTH administration are summarized in Table I. There was a slow gain of 10 pounds in weight (from 145 to 155 pounds) until the beginning of the second week of 80 mg. ACTH daily dosage schedule, when a spontaneous diuresis and loss of 5 pounds occurred. The weight gain was not associated with clinical evidence of fluid accumulation or elevation of arterial blood pressure. There was no further significant change in weight.

Pulmonary Function Studies (Tables II and VI): Prior to the administration of ACTH there was a significant reduction of vital and total capacities with an abnormally large residual air-total capacity ratio, marked diminution of maximum breathing capacity, defective distribution of gas in the lungs, with only moderate disturbance in the integration of alveolar ventilation and perfusion and a normal alveolar diffusing capacity for oxygen. These findings are consistent with pulmonary fibrosis, bronchiectasis and emphysema.

There were some minor fluctuations in the results of the pulmonary function studies performed during and following prolonged administration of ACTH; however, no definite beneficial effects could be ascribed to it, except possibly for a moderate increase in maximum breathing capacity. This fell to the control level during the fifth week after discontinuance of ACTH. It did not change significantly during the next five weeks that it was measured. The observed variations in the total lung volume are consistent with periodic fluctuations in the accumulation of secretions in the bronchial tree with bronchiectasis. It is noteworthy that the residual air total lung volume ratio did not

change even though there was considerable variation in the total lung volume.

CASE V. *Diagnosis: pulmonary emphysema.*

E. C., a seventy-five year old white male, was admitted to the Goldwater Memorial Hospital on March 29, 1948, complaining of increasing shortness of breath on moderate exertion, orthopnea, cough productive of about 2 to 3 ounces of non-foul mucopurulent sputum daily, since early 1936. He was hospitalized many times for these complaints and also for attacks of bronchopneumonia. There was no history of allergy or of asthma. There was a history of chronic alcoholism to which an enlarged liver present from 1938 through 1941 was ascribed. He underwent thyroidectomy for thyrotoxicosis in 1938. Progressive deafness was noted since 1936.

At the time of admission to the hospital he appeared malnourished, chronically ill, became short of breath on slight effort, exhibited orthopnea requiring four pillows but was not cyanotic. The trachea was in the midline; the thyroid was not palpable. There was an increase in the anteroposterior diameter of the chest and subcostal angle with prominence of the sternum. The chest was almost completely fixed in an nispiratory position and moved only slightly with the aid of accessory muscles of respiration. The lung fields were hyper-resonant throughout, breath sounds were distant and there were occasional expiratory squeaks. The heart was not enlarged, sounds barely audible and there were no murmurs. The arterial blood pressure was 170/70. The liver and spleen were not palpable. There was no edema, cyanosis or clubbing.

On teleroentgenographic examination there were signs of advanced pulmonary emphysema with bleb formation. The heart was small. The right ventricular outflow tract appeared prominent on fluoroscopic examination. An electrocardiogram exhibited peaked P waves in leads II and III, left deviation of the electrical axis and normal sinus rhythm. There was 6.5 million red blood cells, and 7,000 white blood cells per cu.mm. of blood and 15.5 gm. of hemoglobin per 100 cc. of blood. The differential count was normal. The urine exhibited no abnormalities.

During the twenty-seven months that the patient was observed in the hospital prior to the administration of ACTH his symptoms were not relieved by expectorants, sedatives and aminophylline. He experienced transient relief from short periods of oxygen inhalation. The only new complaint which developed was tightness in the chest. His course was uneventful except for bronchopneumonia in March, 1950. There were no new findings on physical and roentgenographic examinations of the lungs and heart and the electrocardiographic pattern was unchanged. The clinical laboratory findings were unchanged. The sputum was generally scanty, non-foul, watery or mucoid with green flecks. It did not contain pathogenic organisms.

TABLE VI
CASE IV

Period	Week	Maximum Breathing Capacity (L./min.)—(93.5)*	Vital Capacity (ml.)—(3,520)†
Control	1	38.6	2,090
Water		33.4	2,410
ACTH	2	39.7	1,400
		49.0	1,810
	3	51.0	2,740
	4	57.0	3,280
	5	49.7	2,600
			2,250
	6–8‡	44.6	2,400
Control	9–12‡	45.1	2,550
	13–17‡	35.1	2,230

* Predicted value (7).

† Predicted value for recumbent position (7). Observations were made in erect position where predicted values are probably 5 to 10 per cent higher.

‡ Inclusive.

The patient received 1 cc. of sterile water intramuscularly four times a day from June 22nd through June 30th prior to the administration of ACTH. During this period there was no significant subjective or objective improvement. His weight fell from 101 to 96 pounds.

Ten mg. of ACTH were administered four times daily from July 1st through July 6th in place of sterile water. On the second day he began to complain of increased shortness of breath. On the seventh day there was one plus edema of the feet and ankles; and since the patient felt worse, ACTH was discontinued. There were no new lung or cardiac findings and a gain of only 3 pounds in weight had occurred. He was unwilling to cooperate in pulmonary function tests any more.

The edema disappeared three days after ACTH was discontinued. The increased respiratory distress lasted for about ten days during which time there was a loss of 3 pounds in

weight. The hematologic and metabolic studies carried out before, during and following ACTH administration are summarized in Table I.

Pulmonary Function Studies (Table II): Studies first carried out in October, 1949, indicated the presence of advanced pulmonary emphysema characterized by ventilatory and distributive disturbances, decreased alveolar diffusing capacity for oxygen and moderate impairment in the integration of alveolar ventilation and perfusion. When the studies were repeated approximately eight months later (June, 1950), it was apparent that further deterioration of pulmonary function had occurred. Perhaps most noteworthy was the apparent increase in the proportion of poorly ventilated and well circulated alveoli resulting in a much larger estimated proportion of venous admixture. Results of maximum breathing capacity tests are not shown in a separate table. The average values during both periods of study were the same: 16.2 L. per minute which is 42 per cent of the predicted value.

COMMENTS

The beneficial effect of ACTH in certain diverse clinical conditions suggests the existence of basic mechanisms of tissue injury and of bodily reaction common to them. The increased level of circulating adrenal steroids which follows ACTH administration have been implicated in the bodily defense.[22] In allergic states these steroids have been reported to inhibit histamine formation and also to accelerate its breakdown.[23] It has become increasingly apparent that suppression of the manifestations of disease rather than cure occurs during ACTH administration.

In those diseases of the lungs which have been reported to respond to ACTH the physiologic disturbances have not been thoroughly studied. It is of interest to contrast the different responses to ACTH in the patients on the basis of historical, clinical and physiologic investigations.

Relief from chronic status asthmaticus in patient W. H. within two days after the start of ACTH administration was dramatic and accompanied by a feeling of well being bordering on euphoria. There was also prompt improvement in pulmonary function and it is apparent that this continued to improve over several days. (Tables II and III.) Just before the first course of ACTH was discontinued the only ventilatory disturbances which remained were those of moderate degree of pulmonary emphysema. (Table II.) The manifestations of obstruction to expiration had long disappeared and alveolar ventilation-perfusion relationships were now normal. These observations illustrate that obstructive asthmatic breathing may impair not only alveolar ventilation but also the integration of alveolar ventilation and perfusion. It is reasonable to assume that the residual manifestations of a moderate degree of pulmonary emphysema reflect structural changes in the lungs and thoracic cage secondary to long-standing obstruction to expiration. It is surprising that a greater degree of damage was not evident in view of the twenty-year history of seasonal asthma and almost continual asthma during the two years while in the hospital.

After maximal beneficial effects from ACTH appeared to have been attained, injections of ACTH were discontinued. When after sixteen days it was apparent that the patient had regressed to his previous asthmatic state, sterile water was injected in the same manner as ACTH had previously been administered. During this period of seven days the patient failed to exhibit any subjective or objective improvement. When ACTH injections were substituted for sterile water, the response was as dramatic and prompt as when it had previously been given. Within eighteen hours after the first injection asthma was considerably less intense, the patient felt stronger and was in a happier frame of mind. There was a slowly progressive increase in vital capacity and maximum breathing capacity over the following month. (Table III.) Asthmatic attacks did not recur after fifteen hours following resumption of ACTH administration. However, the lungs were not free of asthmatic physical signs until the tenth day. In all respects pulmonary function studies revealed virtually as good a remission as previously.

Patient H. R. was selected for study in view of his long-standing history of asthma complicated in the past by congestive heart failure. At the time of the study he was not in congestive heart failure, though there were clinical, roentgenographic and electrocardiographic indices of right ventricular strain. It was postulated that if it were possible to ameliorate some of the pulmonary physiologic derangements, right heart strain might be relieved. Weighing heavily against this was the likelihood of causing further embarrassment to the heart by the retention of sodium chloride and water which sometimes accompanies ACTH administration. During the period when 80 mg. of ACTH were administered daily the patient continued to experience asthmatic attacks almost daily. These were relieved by adrenalin given subcutaneously. There was no consistent improvement in the pattern of breathing and lung signs. There was a gain of 7 pounds during the first week believed to be due mainly to fluid retention. This was not accompanied by frank signs of increasing heart failure. Because of the possibility that the therapeutic failure resulted from excessive fluid retention with the 80 mg. ACTH daily dose, observations were repeated at a later date when on a 40 mg. daily dose. Again, no beneficial effects were noted. Weight gain was not as marked.

The results of the pulmonary function tests while the patient received 80 mg. of ACTH daily might suggest a modest beneficial effect in view of an early improvement in the maximum breathing and vital capacities. (Table IV.) The decrease in maximum breathing capacity after the initial rise may have been due to increasing fluid retention secondary to ACTH administration. It is noteworthy that on many days when the patient was not receiving ACTH the results of the maximum breathing and vital capacity tests were as good as and often better than his best performance while receiving the medication. This may have been due to adrenalin injections sometimes prior to the tests or to spontaneous variations in the severity of the asthma.

It is of interest to summarize the outstanding differences between patient W. H. who exhibited excellent reversal of physiologic derangements while on ACTH and patient H. R. in whom no improvement was noted. The latter suffered from recurrent asthmatic attacks all year round since early childhood, exhibited more marked thoracic cage deformity, paradoxical respiratory movements of the lower one-half of the chest and more advanced pulmonary dysfunction, showed evidence of right heart strain and had a past history of congestive heart failure. The former suffered from seasonal asthma for twenty years (since the age of thirty) prior to admission to the hospital and during the last two years while under observation was more or less continually incapacitated by intense asthma with many daily acute exacerbations. His thoracic cage exhibited only a moderate increase in anteroposterior diameter and there was moderate kyphosis of the dorsal spine. The results of pulmonary function studies prior to ACTH administration indicated the presence of advanced emphysema. There was no history or signs of right heart strain.

In view of the reported instances of ACTH altering pulmonary tissue response to chemical (beryllium) and infectious agents (pneumococcus and atypical viral pneumonia), it was of interest to carry out studies in patient D. T. who was suffering from chronic bronchiectasis, fibrosis and emphysema subsequent to arrested bilateral upper lobe tuberculosis. It seemed that ACTH might help to promote better drainage of the bronchiectatic areas and retard the development of fibrosis and compensatory emphysema by its stimulation of phagocyte production,[24] its anti-hyaluronidase effect[25] and its tendency to retard fibroblast proliferation.[26] The patient failed to exhibit any beneficial effect from ACTH administered over seven weeks. He experienced a feeling of well being to a limited extent only during the first several days of ACTH administration. There was improvement in appetite and gain in weight which was in part due to fluid retention. During

the last week of ACTH administration the patient appeared ill for three days and ran fever up to 103°F. associated with increased cough and expectoration. It was feared that reactivation of pulmonary tuberculosis might have occurred. Fortunately, this was not substantiated by the subsequent clinical and laboratory examinations.

Previously reported limited experience with ACTH in Boeck's sarcoid has not been encouraging.[2] The one patient (I. R.) with proven Boeck's sarcoid whom we observed exhibited a dramatic response characterized by defervescence, disappearance of stiffness and swelling of joints and subcutaneous and eyelid nodules, and healing of an indurated ulcer resulting from Kveim antigen. There was improvement in those aspects of pulmonary function which were impaired during the previous control period. (Tables II and V.) Roentgenographic studies of the lungs did not demonstrate shrinkage of the enlarged hilar lymph nodes. In view of the evident clearing of the eyelid and subcutaneous lesions it is possible that improvement in pulmonary function may have resulted from resolution of sarcoid infiltrations not apparent in the roentgenograms. The lack of correlation between physiologic dysfunction and roentgenographic appearance of the lungs is well known.

Objective evidence of improvement during ACTH administration is generally associated with a feeling of well being. In spite of obvious clinical improvement our patient became increasingly reticent and depressed although she continued to cooperate willingly in the studies. After ACTH was discontinued there was a prompt resurgence of the clinical signs of activity of Boeck's sarcoid, mental depression increased and soon culminated in suicide. Unfortunately, the patient's mental state had prevented repetition of pulmonary function studies.

Patient E. C., who suffered from pulmonary emphysema secondary to changes with age, was selected for study because he exhibited disturbances in pulmonary function of similar nature and severity as patient W. H. It will be recalled that in patient W. H. pulmonary emphysema accompanied chronic asthma and he experienced striking improvement during ACTH administration. In contrast, respiratory distress and dependent edema developed in patient E. C. during ACTH administration. From the studies in these two patients it is apparent that the response to ACTH cannot be predicted from the pattern of disturbance of pulmonary function.

SUMMARY

Studies of the effect of ACTH on the clinical course, pulmonary function and some metabolic aspects were carried out in five patients suffering from chronic lung disease.

Two of the five patients exhibited striking improvement while receiving ACTH. There was return to normal of nearly all the derangements in pulmonary function, with prompt regression to their previous state on discontinuance of ACTH. One of these patients was a middle aged man with advanced pulmonary emphysema, fibrosis, seasonal asthma for eighteen years and status asthmaticus for the past two years. The other was a young woman with Boeck's sarcoid. Unfortunately this patient's course was complicated by the development of mental depression which culminated in suicide after ACTH injections were stopped.

Two other patients became worse during ACTH administration. This response was thought to be related to fluid retention which taxed their already diminished cardiac reserve. One was a middle aged man with asthma since childhood complicated by pulmonary fibrosis, emphysema and cor pulmonale. The other was an elderly man with advanced pulmonary emphysema.

The fifth patient, an elderly man who suffered from pulmonary fibrosis, bronchiectasis and emphysema secondary to old inactive tuberculosis, exhibited neither benefit nor deleterious effect from prolonged administration of the hormone.

Consistent changes in the pattern of plasma electrolytes and glucose tolerance were not noted.

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Expectoration of Abnormal Substances and Particles Including Parasites*

Their Diagnostic Significance

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In the chapters on sputum in several standard textbooks of clinical pathology the subject matter is limited to bacteria, fungi, elastic fibers, Curschmann's spirals, Charcot-Leyden crystals and a few other substances. In the past few years, I have encountered a number of cases in which patients expectorated, either in the sputum or directly, other substances or particles which were directly related to the nature of the underlying disease.

CASE REPORTS

CASE I. E. W., a woman aged seventy, was admitted to the Beth Israel Hospital in November, 1946. She stated that since January she had been coughing with an expectoration of yellowish sputum flecked with black particles. Physical examination showed a persistent rhonchus over the right chest. Roentgenograms showed fine nodular infiltrations throughout the mid-portion of the right lung. Bronchoscopic examination revealed the right upper lobe bronchus to be stenosed by inflamed granulation tissue. Through a small ostium, anteriorly, thick pus could be seen. The opening was dilated and pigmented granulation tissue was removed for biopsy. The lumen was patent after this. Biopsy showed a caseous anthracotic lymph node impinging upon bronchial tissue; characteristic tuberculous granulation tissue containing acid-fast bacilli was present.

Comment. This was a case of perforation of a tuberculous lymph node into a bronchus. In elderly patients with this condition anthracotic particles from the lymph nodes often are carried to the bronchial mucosa where they may be visible endoscopically. Although carbon particles were not demonstrated in this patient's sputum, it is reasonable to assume that the black particles described by her actually were carbon. In the text other conditions in which this may happen are described.

CASE II. M. S., a woman aged twenty-seven, was admitted to the Beth Israel Hospital because of frequent hemoptyses of three months' duration. Roentgenographic examination disclosed atelectasis of the lingula of the left upper lobe. There were calcifications at the hilus of the left lung. Bronchoscopic examination showed narrowing of the left main bronchus just below the orifice of the upper lobe bronchus. Bronchography showed the bronchus to the lingula to terminate abruptly about one-half inch from its origin. The patient was discharged with a diagnosis of broncholithiasis. Several months later word was received from her physician that the patient, on visiting, had presented him with a small broncholith which she had suddenly expectorated.

Comment. The expectoration of the broncholith confirmed the clinical diagnosis which had been made previously.

CASE III. L. L., a man aged thirty-eight, was treated in the Beth Israel Hospital in 1931 for a mediastinal abscess complicated by left-sided empyema. He had previously had other metastatic manifestations of chronic staphylococcemia. In 1935 he developed osteomyelitis of the eleventh thoracic vertebra. He was sent home to continue treatment. He was readmitted one year later for pneumonia. He stated that during

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the interim he had had hemoptyses and had also expectorated pieces of bone.

Comment. Undoubtedly, the suppurative process in the spine established communication with the bronchial tree through the pleura and lung, enabling the sequestrum of bone to be expectorated.

CASE IV. M. J., a man aged sixty, was treated in the Beth Israel Hospital in 1944 for a left empyema which cleared up. Continued observation in the outpatient department showed a persistent confluent shadow in the roentgenogram of the left lung which had the ground-glass appearance of lipoid pneumonia. It was then learned that every day for twenty-seven years the patient had taken two tablespoonfuls of mineral oil before breakfast and before retiring. The sputum was then searched and typical oil droplets were discovered.

Comment. The discovery of oil droplets in this case confirmed the diagnosis of lipoid pneumonia.

CASE V. D. P., a man aged sixty-two, was treated in the Beth Israel Hospital in April, 1949. He had had a "virus pneumonia" in 1946. Since then he had a persistent cough and sometimes had expectorated "black" particles. Since June, 1947, he had hemoptysis almost every month. For the past year he had wheezing. In January, 1948, a physician noted a shadow in a roentgenogram of the patient's right lung. A recent film taken elsewhere showed a circumscribed homogeneous mass the size of an orange in the right lower lobe. He then was referred to the hospital. Bronchoscopy showed the right lower lobe bronchus, at the level of its apical branch, to be obliterated by a bluish-black polypoid mass growing proximally up from the depths. It bled profusely. Biopsy revealed a malignant melanoma. Thorough search of the patient's body by available clinical methods failed to reveal a primary site. A pneumonectomy was performed to which the patient succumbed. Unfortunately, permission for necropsy was not granted.

Comment. It is reasonable to assume that the black particles described by the patient were fragments of the melanoma which might have been identified histologically.

OBSERVATIONS

A study of the literature and textbooks reveals many similar situations. Altogether there is a surprisingly long list of substances the expectoration of which is not only of diagnostic significance but is often pathognomonic of a specific disease. These will be set forth below. Bacteria, fungi and cytologic diagnosis of malignancy will not be included.

Caseous Particles. Perforation of tuberculous lymph nodes into bronchi usually is seen in children, less commonly in adults. The diagnosis is generally proven by endoscopic examination (Case I). Occasionally, the patient will expectorate small whitish particles which on histologic examination are found to consist of caseous material, thus establishing the diagnosis. One such case was reported by Hartung[1] and three by Steiner and Geissberger.[2]

Broncholiths (Lung Stones).[3,4] Expectoration of stony particles is quite common. These vary in size, shape and consistency. They are grayish white in color and may be single or multiple. They usually are hard and gritty, occasionally soft and putty-like. They customarily have a rough surface but may be faceted when the stones are multiple. Chemically, they consist of calcium phosphate 85 to 90 per cent and calcium carbonate 10 to 15 per cent.

In most instances they are the result of perforation of previously calcified tuberculous lymph nodes into bronchi. The sharp-edged spicules burrow mechanically until they reach the bronchial lumen. They may then be expectorated spontaneously (Case II). Often they must be removed endoscopically. In a review of seventy-one reported cases of broncholithiasis by Zahn[5] thirty-five gave a history of spontaneous expectoration of stones. Less frequent causes are prolonged suppuration and deposition of calcium around foreign bodies.

Carbon Particles. 1. *Perforating tuberculous nodes:* In aged persons there may be reactivation of a dormant tuberculous infection in the mediastinal nodes which results in gradual perforation of the nodes into

large bronchi. These nodes generally are anthracotic and particles of carbon are carried to the bronchial mucosa where they can be seen endoscopically. Arnstein[6,7] was able to demonstrate the carbon particles in the sputum in many such cases.

2. *Anthracosis:* Arnstein[6] noted that expectoration of black particles also is seen in cavernous tuberculosis with severe anthracosis. Dreessen and Jones[8] described black viscid sputum in anthracosilicosis. Gooding[9] described a similar type of sputum in cases of anthracosilicosis in which necropsy showed a crumbling of the involved portions of lung; in only 25 per cent was the crumbling due to tuberculosis.

Asbestos Bodies.[10] In asbestosis characteristic asbestos bodies are found in the sputum. The body consists of a core of asbestos fiber surrounded by iron-containing protein deposits. These are golden yellow in color and do not stain with ordinary histologic stains but show a brilliant blue with potassium ferrocyanide. They are variable in form and size and characteristically are slender, elongated segmented structures with bulbous ends which give them a dumbbell or drumstick shape. They range in length from 10 to 180 μ, with an average of 35. The incidence of the bodies increases with added exposure.

Foreign Bodies. Jackson and Jackson[11] state that a large light foreign body occasionally may be coughed out, usually long after lodgment, and when loosened by secondary suppuration. The bodies most likely to be expectorated are those which are cubically shaped, particularly teeth. Three per cent of nut kernels are coughed up spontaneously; pins rarely are.

Food.[12] In cases of broncho-esophageal fistula, whether congenital or acquired, the patient rarely may expectorate some of the ingested fluid. A case was reported each by Clerf[13] and Claggett and Schmidt.[14] I have also seen expectoration of food particles in a patient who underwent general anesthesia shortly after a meal. She aspirated some regurgitated food and for several hours thereafter expectorated identifiable food particles.

Hair.[15] Dermoid cysts of the mediastinum occasionally rupture into bronchi. The patient then may expectorate the contents of the cyst, consisting of hair, cholesterin crystals and fat droplets. Morris[16] described a case in which the expectorated hair was found to have a lighter color than the patient's own. Expectoration of hair is pathognomonic of a ruptured dermoid cyst.

Bone. Case III illustrates the erosion of a bone sequestrum from osteomyelitis of the thoracic spine through the pleura and lung into the bronchial tree. I have seen another such case at Montefiore Hospital. In this case the patient developed a secondary mediastinal abscess which was drained surgically. Several months later the patient expectorated a spicule of bone. I have been unable to find reports of similar cases in the literature.

Chyle. Chylothorax is a rare condition. Most cases are caused by trauma. Most nontraumatic cases are the result of neoplasms. Very rarely, as a result of pleuropulmonary perforation, chyle is expectorated. Cases in which this occurred were reported by Campbell[17] and by Lammers.[18]

Oil. 1. *Oleothorax:* Matson[19] described pleuropulmonary perforation in oleothorax with expectoration of oil. This is relatively infrequent. The expectoration often includes purulent exudate. Howlett[20] states that the perforation sometimes is preceded by an increased amount of thin, watery or mucoid sputum which then is followed by the oil droplets.

2. *Lipoid pneumonia:* Schneider[21] states that the diagnosis in this condition often may be established by discovery of oil droplets in the sputum. Several days after the patient has stopped taking mineral oil he expectorates into a clean wide-mouthed jar before breakfast for three successive days, after thoroughly washing his mouth and throat with saline. Cigarette or lens paper placed on the surface brings out the tell-tale grease spots on the paper. The sputum is also examined under the microscope. Min-

eral oil droplets take the characteristic stain with scarlet red. Saponifiable fats and oils take an osmic acid stain. Case IV is an example of this. It should be remembered, however, that in many cases of lipoid pneumonia the oil becomes surrounded by dense fibrous tissue, forming a kind of paraffinoma. In these cases no oil droplets are expectorated. A negative examination, therefore, does not exclude the diagnosis.

Fat.[22–24] The presence of fat in the sputum in cases of fat embolism following fractured bones is of great diagnostic importance. The fat is found between thirty-six to seventy-two hours after embolization has occurred. Scott, Kemp and Robb-Smith[25] describe a method for detection of fat which was first suggested by Warthin: (1) Make a thin smear of the sputum (by squeezing between two slides) covering two-thirds of the surface of the slides. (2) While the smear is still wet, flood the slide with Sudan IV solution and leave for three minutes. (3) Rinse in tap water. (4) Counterstain with hematoxylin solution for three minutes. (5) Rinse in tap water. (6) Differentiate if necessary in 10 per cent acid alcohol. (7) Blue in tap water. (8) Mount in Apathy's medium or glycerine jelly. The Sudan is a saturated solution of Sudan IV in equal quantities of acetone and 70 per cent ethyl alcohol. The fat is in the form of extracellular globules 10 to 40 μ in diameter. Histiocytes containing fat globules are said to be found in many chronic pulmonary diseases. In aspiration pneumonia striated muscle fibers are found in addition to extracellular fat.

Bronchial Casts.[26–28] Most textbooks describe the rare phenomenon of expectoration of bronchial casts. These range in size from fragments one-half inch long to complete casts 7 inches long with a branching pattern corresponding to divisions of the bronchi. Casts from larger bronchi are hollow and present a laminated appearance as a result of successive deposits of fibrin and mucus. The smaller casts are solid and often terminate in spirals. They consist mainly of fibrin and sometimes also of mucus. They are found in a rare condition known as fibrinous bronchitis. Very little is known about the pathogenesis. Following expectoration of the casts the patient generally makes a good recovery.

Curschmann's Spirals and Charcot-Leyden Crystals.[29] These bodies are found chiefly in bronchial asthma. They are described in most textbooks. Curschmann's spirals are whitish or yellow, wavy threads, frequently curved into little balls. The length rarely exceeds 1.5 cm. but may reach 5.0 cm. They may sometimes be seen with the naked eye. They appear under the microscope as mucous threads with a bright colorless central line about which are wound many fine fibrils. These are loosely or tightly wound. Eosinophiles usually are present within the spirals.

Charcot-Leyden crystals are colorless, pointed and often needle-like. They are hexagonal on cross section. The size varies greatly. The average length is three to four times the diameter of an erythrocyte. They may be absent in freshly-expectorated sputum but appear in large numbers after the specimen has been standing. Samter[30] recently has shown that the crystals are derived from eosinophiles.

Carcinoma. A discussion of the recent important advances in the cytologic examination of the sputum for malignant cells is beyond the scope of this paper. It has been noted,[31–33] however, that on rare occasions a fragment of tissue is found in sputum which, by histologic examination after embedding and sectioning, shows the typical malignant changes. A diagnosis of bronchogenic carcinoma can be established in this fashion.

Melanoma. In Case V, which was a proven case of malignant melanoma invading the bronchus, the patient gave a history of expectorating black particles. In retrospect these very likely were fragments of the tumor mass possibly capable of histologic identification. Melanoma of the bronchus is very rare; in the few reported cases no comparable phenomenon has been mentioned.

Parasites. 1. *Ameba:*[34] Futcher[35] described the chocolate color of sputum in amebic abscess of the liver which had perforated through the pleura and lung into the bronchial tree. This appearance of the sputum has been likened to anchovy sauce and was found in 74 of 153 cases collected by Ochsner and DeBakey.[36] The color is due to chemical alterations in blood derived from lung. The sputum is found to contain hematoidin crystals, cytolized liver tissue, pus cells, elastic tissue and, most important, Entameba histolytica. The specimen must be moist and warm when examined for the parasite.

2. *Echinococcus:*[37] Pulmonary hydatid cysts frequently rupture into a bronchus. A large amount of clear, salty, alkaline fluid suddenly is expectorated, followed later by smaller amounts. In this fluid may be found the whole parasite or some of its components, namely, scolices, hooklets and pieces of the membranes. Dew[38] and Barrett and Thomas[39] state that it is unusual for daughter cysts to be expectorated under ordinary circumstances. This happens when there has been a partial rupture of the cyst with slight leakage of fluid and no infection. If large numbers of daughter cysts are expectorated and the lesion is in the lower lobe of the right lung, suspicion should be aroused of a rupture of a hepatic cyst through the lung into a bronchus. Detection of bile in the sputum is an important confirmatory test of this diagnosis.

3. *Ascaris:*[40,41] During the life cycle of Ascaris lumbricoides in the human, the larvae pass through the pulmonary capillaries into the alveoli, thence up the trachea and down the food passages. Ordinarily, no respiratory symptoms result. If the infestation is heavy, there may be symptoms and even an ascaris pneumonia. Under these circumstances the larvae very rarely may be demonstrable in the sputum. Girges[42] found this event in only two cases in a very large series.

4. *Strongyloides:*[40,43] The life cycle in the human of Strongyloides stercoralis is similar to that of ascaris. Pulmonary involvement is more frequent and occasionally ova or larvae are found in the sputum.

5. *Paragonimus westermanni:*[40,41] This parasite, also known as lung fluke, has a complicated life cycle. The parasite reaches the human lung where it matures and produces eggs. Clinically it causes chronic cough with the expectoration of sputum streaked with blood and brown flecks. These flecks are the eggs which have a characteristic operculated appearance. Musgrave[44] noted that occasionally the adult worm also is found in the sputum. Miller and Wilbur[45] reported three cases in soldiers who served in the South Pacific area in the recent war. Tillman and Phillips[46] reported ten cases in Phillipine guerrilla troops. They pointed out that the parasites are seen best in unstained smears and that it is often necessary to examine many specimens.

6. *Syngamus trachealis:*[40,41,47] Very little is known about the life cycle of this parasite. It belongs to the genus Cyathostoma and is common in certain avians. Eight cases of human infestation have been reported. The parasite apparently inhabits the trachea; following violent coughing it may be expectorated. Characteristically, two male or female parasites are permanently joined in pairs.

7. *Mites (Acarina):* In a series of papers, Carter and his co-workers[48,49] reported the finding of a high incidence of mites in the sputum of cases of asthma and bronchitis in Ceylon. A high eosinophilia was present in these cases. The mites were of the genera Tarsonemus, Tyroglyphus or Carpoglyphus. Administration of arsenical drugs resulted in both clinical improvement and partial or complete elimination of the mites. The sputum specimens were collected under stringent precautions to avoid outside contamination. The method of examination follows: Treat the sputum with an equal quantity of 1 per cent potassium hydroxide. Shake the specimen and allow to stand until the mucopurulent material has disintegrated. Add 5 to 10 drops of Löffler's alkaline methylene blue and shake. Add formalin sufficient to make a 10 per cent con-

centration. Allow the specimen to stand for eighteen to twenty-four hours, then centrifuge. Examine the sediment microscopically.

Other authors[50,51] reported similar findings. Recently, Wiswanathan[52] assembled cases reported under various names which were characterized by bronchopulmonary symptoms and signs, high eosinophilia and therapeutic response to arsenicals. He assigned the name pulmonary eosinophiliasis. He stated that other authors and himself had failed to confirm the presence of mites in these cases and questioned the validity of the previous work. Thus the matter stands at present.

SUMMARY

In many intrathoracic diseases an abnormal substance or body will occasionally be expectorated either directly or in the sputum. The detection of this substance is not only of diagnostic significance but is often pathognomonic of that disease. A list of such substances which have been considered in this article includes: caseous particles, broncholiths, carbon particles, asbestos bodies, foreign bodies, food, hair, bone, chyle, oil, fat, bronchial casts, Curschmann's spirals, Charcot-Leyden crystals and malignant tumor masses. Also, the following parasites are considered: ameba, echinococcus, ascaris, strongyloides, Paragonimus westermanni, Syngamus trachealis and mites.*

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Review

Pathogenesis of Hypertension*

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IN a symposium conducted by The American Journal of Medicine on the subject of arterial hypertension[1] a number of studies and reviews were presented which described some of the modern concepts of the disease and its various ramifications. Attempts to integrate the several concepts leave one somewhat confused, however, by the different points of view expressed. Understanding of the condition has progressed rather rapidly during the last fifteen years. Enough evidence is now at hand to formulate a tentative hypothesis and to organize the experimental and clinical facts in such a way as to arrive at a theory which will satisfy most of them.[2] The purpose of this report is to develop such a hypothesis, to examine it and to evaluate it in the light of known facts and suggestive mechanisms.

Arterial hypertension, especially that variety called "essential," is a psychosomatic disorder. Therefore, it is necessary to examine first in what way the psyche differs from "normal"; second, in what way the psyche influences the soma; and third, in what way the soma responds to such influences. The various pathways through which these influences can act and the immediate and long term effects of their action must be considered closely. Furthermore, examination must be made of the several mechanisms by which a condition such as hypertension may be maintained, may fluctuate in intensity and may finally change in a direction incompatible with life.

The influences and their interaction will be discussed in the order in which they appear to act. They include: first, the influence of the psyche and of the nervous system, which appear to be common underlying etiologic factors; second, sustaining factors, which include neurogenic, nephrogenic and adrenocorticogenic influences concerned in maintaining elevation of the blood pressure; and third, the consequent effects of chronic hypertension to cause pathologic changes in arterioles. In addition an attempt will be made to indicate gaps in basic knowledge, the filling of which is necessary for a thorough understanding of these important and prevalent diseases. Various pathogenetic clinical types will be described. Those forms of arterial hypertension believed to be secondary to other conditions, e.g., disturbances of the endocrine glands (such as adrenal tumors), renal excretory insufficiency (from obstruction, glomerulonephritis or pyelonephritis) and types due to congenital anomalies (such as coarctation of the aorta) or to collagenous diseases (such as polyarteritis nodosa) will be considered only insofar as they contribute to our understanding of "essential" hypertension.

ETIOLOGIC FACTORS

Psychogenic Factors.† There appears to be present in practically all cases of primary arterial hypertension certain alterations of personality which are quite consistent. These disturbances have not been fully appreciated

† "Psychic" and "neurogenic" are fairly definite terms describing certain areas believed to be important in etiology. A more inclusive but less well defined term is the "constitutional factor."[2] It would not be amiss to speak of the "hypertensive diathesis" as that combination of conditions, hereditary, psychic, nervous and vascular, which predisposes an individual to the development of hypertension and/or the ability to react to stresses by means of vasoconstriction.

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until recently, although for many years the "nervousness," "tenseness" and emotional lability of hypertensive patients has been noticed. Under modern conditions in this country 40 to 50 per cent of the population appears to develop hypertension at some period of life, usually after the age of forty.[3] If, as recent studies suggest, there is a disturbance or deficiency in the personalities of such individuals, the frequency of this deficiency does not make it a normal state.

Evidence for disturbances of personality is found in three fairly extensive surveys. Weiss, studying ninety-three patients suffering from "essential" hypertension, concluded that emotional factors were chiefly related to the onset of hypertension in fifty-three, and related in a minor way in thirty-three.[4] In only seven cases was there apparently no relationship. Like others, he found that inhibited aggression ("chronic rage") was of great importance and suspected some specific relationship of this disturbance to hypertension. Binger et al.[5] found that a group of twenty-four hypertensive patients carefully studied as to life history and personality showed a particular psychologic configuration. The outstanding elements were "exaggerated dependent strivings, submissiveness coupled with stubbornness, feelings of weakness and defenselessness, suppression of hostility, fear of injury and emotional detachment. In addition, there was a tendency to develop acute emotional disorders characterized mainly by anxiety and depression and often associated with temporary failure of the usual techniques of mastery of the environment. This acute failure of the integrative functions of personality seems to result from the inefficiency of the patterns of defense against anxiety and a weakness of the repressive mechanisms."

The third study was made at this institution by Gressel et al.[6] Six elements of the personality were particularly singled out for examination. Fifty hypertensive patients, fifty patients suffering from psychoneuroses without hypertension and approximately an equal number suffering from chronic diseases not believed to be psychosomatic and with normal blood pressures were included. Objectivity in the evaluation of personalities was stressed and the results analyzed statistically. Of the facets of the personality which Binger described only two were found to be significantly predominant in the hypertensive group: obsessive-compulsive tendencies and subnormal assertiveness. Anxiety and hysteria occurred frequently and similarly in both hypertensive and psychoneurotic patients to a significantly greater extent than in the other group. Impulsive traits were present with similar frequency in all groups, and no significant trends were found for the traits of excessive insecurity, depression and frustrated ambition. While it is impossible to quantitate a subjective impression, it is possible to ascertain by some of the better psychologic methods whether certain qualities are present or not, and to a certain extent to what degree they are present. Therefore, the implications of these two latter studies are that certain personality defects not common to the general population are present in individuals who develop hypertension. The extent of these defects varies considerably from person to person. Similar personality structures were found by Wolf et al.[7] using a group of asthmatics as controls.

Are these disturbances of personality secondary to hypertension or are they concerned in its causation? One-third of Binger's cases were in early mild stages of the disease. In addition, "evidences of this peculiar structure of personality are discernible before hypertension, or its prodromal symptoms, make their appearance."[5] The same conclusions could be drawn by Gressel, for the manifestations of the "hypertensive personality" were present to an equal degree in early mild and late severe cases, and antedated by many years the onset of hypertension.[8] Therefore, it is improbable that the changes were the result of hypertension; their presence implies a causal relationship. It is not known whether defects of personality such as these are acquired, that is, developed during childhood, youth

and possibly adult life, or whether they are inherited. Our own view of the matter is that these defects are developmental, a result of either the stresses of the modern environment or of one considered hostile by the individual, and presenting problems incapable of solution with the capabilities at hand.

For the moment, therefore, let us assume that defects of personality of a specific nature exist which are in themselves conducive to conflict when an unfavorable environment impinges upon the psyche. This, of course, is common to everyone. The manner in which nervous tension resulting from the repression of these conflicts is resolved is not the same in all individuals. In those predisposed to hypertension, however, it would appear that the sympathetic nervous system and in some the adrenal cortex respond to or are activated by these repressed conflicts. It would also appear that this method of reaction occurs in from 40 to 50 per cent of the population. Variations in degree, type and severity of reaction in different individuals suggests that this factor has wide differences of intensity while showing a common pattern.

The habit of transferring these conflicts to the autonomic nervous system probably becomes more firmly established as the years pass. Major calamities may be necessary to evoke reactions in most younger individuals; however, as this habit of reacting becomes established the trigger mechanism may be set off by smaller and smaller stimuli, and those minor irritations which are present in the lives of all of us become major ones insofar as their effects upon the body are concerned. According to this concept, hypertension is a disorder resulting from the socio-economic complexities of modern civilization and the stresses and conflicts which they impose upon man who is trying to adapt. Hypertension is therefore one of the prices man must pay because of his own deficiencies in coping with the environment of the civilization he has devised for himself. Because that civilization has resulted in conflicts which are beyond his capacities for solution by himself, a state of imbalance of his vegetative functions has resulted which leads to disease.

Hereditary Factor. An hereditary factor is suggested by the work of Hines[9] who found hyper-reactivity of the vascular system to a painful stimulus (cold pressor test) a familial trait which predisposed to hypertension. Over 40 per cent of the off-spring exhibited vascular hyper-reactivity when one parent had hypertension or hyper-reactivity; when both parents were either hypertensive or hyper-reactors, 95 per cent of their children showed this trait. When both parents were hypertensive, about 90 per cent of their children eventually developed hypertension. That the hereditary trait is not a prerequisite is suggested, however, by the absence of a familial history in over half of cases of hypertension.

Neurogenic Factor. The neurogenic factor is mediated by that portion of the nervous system which reacts by peripheral manifestations to conflicts produced in the psyche. The essential parts involved in hypertension appear to be the hypothalamus and the sympathetic nervous system. While the exact pathways by which cortical impulses travel to the hypothalamus and the mechanisms by which conflicts can set off emotional discharges are not thoroughly understood, the end results of such discharges initiated by the cortex are well known. For some reason, either through development or inheritance, patients subject to hypertension appear to react to emotional tension and to conflicts by means of a discharge of the sympathetic nervous system. It is possible that this method of reaction, the result of internal "boiling over," is an inherited defect; other portions of the population may react to analogous situations of conflict through, for example, the parasympathetic nervous system. An understanding of any psychosomatic disease involves not only a knowledge of the psyche and the soma but especially of the connections between them, of their effects and of their controls in the brain and by endocrine glands.

Evidence for hyperactivity of the sympathetic nervous system in hypertension is for the most part based upon clinical observations and reasoning. Patients in early or prehypertensive stages develop under proper stimuli manifestations suggesting discharges of their sympathetic nervous systems, with peripheral vasoconstriction.[8] The cold pressor test demonstrates hyper-reactors to painful stimuli;[10] hyper-reactors to cold or psychic stimuli usually develop hypertension[11] and sympathetic hyperactivity offers the most probable explanation for this phenomenon. Many hypertensive individuals at times have cold, clammy, intensely constricted extremities, perspire profusely under emotional tension, especially on palms of hands, on feet and in axillae, and show vasomotor instability by means of flushing of the skin and variations in blood pressure and pulse rate. Acute emotional outbursts are occasionally seen, with watering of the eyes, palpitation, tachycardia, a blotchy erythema of the skin of the neck, chest and back, and further elevation of blood pressure. In some cases this tendency is so pronounced as to appear in acute attacks with signs suggesting that the hypothalamus has suddenly discharged via the sympathetic nervous system in a complicated manner not thoroughly understood. This sequence of events has been termed the "hypertensive diencephalic syndrome." The intradermal injection of histamine will produce these discharges in susceptible individuals.[12]

Further suggestive evidence is based upon the observations that autonomic blocking agents will lower blood pressure to varying levels[13] presumably by interruption of neurogenic impulses in ganglia, that extensive sympathectomy sometimes abolishes hypertension for several years, that blood pressure levels may be extremely variable in some hypertensive patients independent of cardiac output[14] and that blood vessels of the extremities are hyper-reactive to minor stimuli.[15,16] The studies which have shown little neurogenic activity in hypertension may have been made in advanced cases; as will be discussed, other factors may operate in them to the partial exclusion of the neurogenic. When neurogenic influences are clinically evident, symptoms, signs and findings strongly suggest a form of sympathetic activity not dependent upon the release of epinephrine but possibly similar to that resulting from the action of norepinephrine. Undoubtedly the peripheral resistance varies in these individuals from time to time.

SUSTAINING FACTORS

Neurogenic* vasoconstriction and its effects can be profound and prolonged. When sympathetic discharges take place or when the sympathetic nervous system is hyperactive for prolonged periods, the cardiovascular and other systems are affected. Of most concern to the problem of hypertension are the effects on (1) blood vessels, (2) kidneys and (3) endocrine organs.

Neurogenic vasoconstriction probably occurs in all organs and tissues of the body to some extent. When this is generalized, blood pressure rises. To what degree each local peripheral bed contributes to the generalized increase in peripheral resistance is not known, but the splanchnic area may be somewhat more labile in this respect than that of striated muscles, for example. Emergency responses of the cardiovascular system mediated through sympathetic nerves and the adrenal medulla are well understood. There is a tendency to shift blood away from splanchnic areas and into those used for emergencies, e.g., muscles. The output of the heart may increase transiently but is soon compensated for by the diminished blood flow resulting from the increased resistance. Renal vasoconstriction occurs and is prolonged.[7] Epinephrine is discharged

* The term "neurogenic" is used in a broad sense, and includes the actions of chemical effector substances acting on the smooth muscles of blood vessels and on organs as well as those resulting from nerve-borne impulses. In this discussion "neurogenic" usually refers to the sympathetic component of the autonomic nervous system with its "adrenergic" effects, although parasympathetic actions and their cholinergic chemical effectors are also "neurogenic."

from the adrenal medulla and the cortex is stimulated either directly or via the pituitary's adrenocorticotropic hormone. Sympathin E, which is probably nor-epinephrine, may be formed in increased amounts or may be activated excessively. The net result can be not only a transient hypertension but one prolonged for many minutes or even hours, with residua lasting much longer, until the reaction wears off or compensatory functions come into play.

The two known chemical effectors of the sympathetic nervous system, epinephrine and nor-epinephrine, have quite different actions. Epinephrine increases cardiac output and decreases peripheral resistance in physiologic doses; minute doses can cause vasodilatation. Nor-epinephrine (l-arterenol) on the other hand acts as a generalized vasoconstrictor substance with little or no effect upon cardiac output.[17] The hemodynamic profile produced by this naturally occurring substance is similar to that seen in chronic arterial hypertension with the exception that pulmonary vascular resistance is increased; in hypertension it is usually but not always normal. Nor-epinephrine could account, however, for part of the mechanism of neurogenic vasoconstriction.

As part of splanchnic vasoconstriction, renal blood flow is reduced, the efferent arterioles of the glomeruli being predominantly affected, although strong stimulation causes constriction of both efferent and afferent arterioles. This reduction may last a long time after epinephrine is injected or vasoconstriction is produced by alarm. The slow return to normal is worthy of emphasis. In Smith's original experiments[18] appreciable reduction of renal plasma flow and increase in filtration rate were noticeable for an hour or longer after the initial emotional or chemical stimulus.

Wolf et al.[7] explored the relation of the psychic to the somatic factor by measuring renal blood flow and arterial pressure before, during and after traumatic interviews concerned with emotional problems. Most of their cases exhibited labile blood pressures which, while often at high levels, still retained the ability to drop to near normal ranges and were therefore not in late stages of the disease. Their studies clearly demonstrated the close dependency of arterial pressure and renal blood flow upon the immediate emotional situation. Discussion of topics involving personal conflicts caused prolonged rises in blood pressure, reductions in renal plasma flow, and renal hemodynamic pictures consistent with those seen in more severe essential hypertension. Studies made over long intervals likewise showed the relation of the environmental situation to the level of blood pressure. The psychoneurogenic mechanism of renal and peripheral vasoconstriction therefore seems clearly established. Furthermore, this pattern of reaction was abolished after lumbodorsal sympathectomy, indicating the sympathicogenic nature of the reaction.

Nephrogenic Factors. While blood pressure in susceptible individuals may rise acutely as a result of generalized neurogenic vasoconstriction, the other functions which control blood pressure more slowly probably account for most of the prolonged changes which occur. The kidneys particularly are implicated. Renal ischemia on a neurogenic basis may cause the kidneys to excrete into the circulating blood humoral pressor substances which act for a long time upon blood vessels, increasing peripheral resistance and raising blood pressure. There are many pressor mechanisms of humoral nature present in the body; at least sixteen different substances have been detected, identified, or believed implicated (Table 1) of which eight are nephrogenic in origin. If nephrogenic substances are active, the results of their actions are known. Until the unknown pressor substance which has been postulated and detected by various methods has been identified chemically we shall call it the *Hochdruckstoff*. It is defined as a substance or group of substances with the following pharmacologic actions: (1) elevation of blood pressure; (2) generalized and relatively equal vasoconstriction of all vascular beds except the pulmonary; (3) renal vasoconstriction greater on efferent

than on afferent arterioles; (4) no pronounced alteration of cardiac output or pulse rate; (5) no obvious sympathomimetic effects (sweating, pallor, spasm of sphincters, etc.); (6) no change in blood volume or blood viscosity. The hypothetic *Hochdruckstoff* is probably concerned in chronic hypertension, maintaining blood pressure at constantly elevated levels superimposed upon which neurogenic mechanisms operate. Prolonged action is unnecessary provided continuous formation is assured. Any naturally occurring substance having these actions is under suspicion as a causative agent in hypertension. Six naturally occurring substances are probably somewhat similar pharmacologically to the *Hochdruckstoff*. (Table 1.)

The best known renal pressor mechanism is the one involving renin and hypertensin. It is not necessary to explain at length the reactions which produce hypertensin, concerning which there is a large literature.[19] Renin, a proteolytic enzyme in kidney, acts on a specific substrate, an α_2 globulin produced probably by liver, called hypertensinogen, to form a peptide, hypertensin. An enzyme in blood, hypertensinase, inactivates hypertensin. The renin pressor mechanism is active in shock, congestive heart failure and acute renal ischemia. Proof of abnormal activity in chronic hypertension is lacking.[20]

TABLE 1

PRESSOR SUBSTANCES POSSIBLY RELATED TO HYPERTENSION

Name	Source	Accessory Conditions	Chemical Nature	Pharmacologic Action	Obtained Pure	Found in Hypertension	Similarity to Hochdruckstoff
Proteins:							
Renin	Kidney	Renal ischemia	Protein	Prolonged	No	Acute	Yes
Prolonged pressor substance	Kidney and blood	Hypotension (Renal ischemia ?)	Protein	Very prolonged	No	?*	Unknown
Peptides:							
Hypertensin	α_2 Globulin	Renin	Peptide	Acute	No	Acute	Yes
Pepsitensin[81]	α_2 Globulin	Pepsin	Peptide	Acute	No	No	Yes (?)
Serotonin	Blood	Standing	Peptide	Acute	Yes ?	No	Unknown
VEM	Kidney	Renal ischemia and anoxia	Peptide (?)	Prolonged	No	Yes	Unknown
Amines:							
"Amines"[82]	Blood	Renal ischemia and anoxia	Amine	Acute	Yes	Yes	Possibly (mixture)
Nor-epinephrine	Tissue	Nervous stimuli	Amine	Acute	Yes	?	Yes ?
Urosympathin[83]	Urine	.....	Amine	Acute	No	Yes	Unknown
v. Euler's[84] substance	Blood and tissues	.....	Nor-epinephrine ?	Acute	No	No	Yes ?
Victor's material[85]	Kidney	Anaerobic autolysis	Tyramine ?	Acute	No	No	Unknown
Pherentasin	Arterial blood	Hypertension (renal)	Amine	Prolonged	Yes	Yes	Unknown
Nicotine Bases:							
Lockett's base[86]	Urine and blood	Renal ischemia	Complex alkaloid	Acute	No	Experimental only	Unknown
Urohypertensin[87]	Urine	.....	Nicotine base ?	Acute	No	Yes ?	Unknown
Others:							
Nephrin[88]	Kidney	.....	Unknown	Prolonged	No	Yes	Unknown
Desoxycorticosterone	Adrenal cortex ?	Salt and hypertension ?	Steroid	Prolonged	Yes	Certain types ?	Yes ?

* Where a question mark (?) is shown, the characteristic of the material is in doubt. It is obvious that the chemical identification and the pharmacology of most of these substances has been insufficiently studied.

Renin is antigenic and to some extent species-specific, and anti-renin in some cases will lower the blood pressure of experimental hypertensive dogs.[21] From the evidence to date it is probable that the renin mechanism acts in a slower and more prolonged manner than other emergency mechanisms, may be concerned in relatively rapid changes in blood pressure which are, however, still slower than those produced by neurogenic vasoconstriction, and may operate at all levels of blood pressure. Renin does not appear to be the primary effector substance in hypertension and, although similar in action, is probably not the *Hochdruckstoff*.

Enough evidence is now at hand to reinforce the belief that other, probably nephrogenic humoral substances are present. The brilliant work of Shorr and his group[22] in demonstrating vasoexcitor and vasodepressor materials acting to maintain normal vasomotor tone has led to the discovery of increased amounts of both substances in the blood of hypertensive animals and human beings. The vasoexcitor material was demonstrated indirectly, the vasodepressor directly. The latter has been identified as ferritin;[23] the former appears in the anaerobic autolysis of kidney and after chronic renal ischemia. It is not hypertensin but its general pharmacology is unknown.

An unidentified substance which we have named pherentasin* has been isolated from the arterial blood of hypertensive patients in this laboratory, using the blood pressure of the intact hypertensive rat for assay.[24,25] When purified, it appears to be present in very small amounts, 10 to 20 γ per L. of blood. The pressor effect of pherentasin on blood pressure of the rat, unlike that of hypertensin, is delayed and prolonged. It contains free amine and carbonyl groups necessary for biological activity, is of small molecular size, non-protein and is probably an amine. Pherentasin is found to a large extent in the blood of patients with the more severe forms of hypertension, especially those who show evidence of minor renal damage, but it has not been proven to be renal in origin. Patients with "neurogenic" hypertension who have little vascular damage exhibit only small amounts in their blood. A depressor substance is also present which resembles pharmacologically and spectrophotometrically an adenyl derivative. The pressor material has a reaction similar to Shorr's vasoexcitor material when his test methods are employed.

Although not a necessary characteristic, substances giving prolonged pressor responses have been of interest in this problem. The vasoexcitor material of Shorr and pherentasin have equally long actions. A prolonged pressor substance has been isolated from the blood of animals in shock; it resembles but is not renin.[26] Other substances under suspicion are: nor-epinephrine which acts in many ways similarly to the theoretic *Hochdruckstoff*,[17] serotonin isolated from red blood cells[27] and amines. It has been shown that ischemic kidneys decarboxylate but do not deaminate certain amino acids;[28] the amines so formed are pressor and are oxidized by a specific amine oxidase.[29] "Amines" are increased above normal levels in extracts of hypertensive blood;[24,25] this abnormality may represent a defect in the metabolism of certain amino acids, without reference to a specific pressor amine. None of these substances has been closely identified with human hypertension to date. (Table 1.) The similarity of the action of nor-adrenalin to the *Hochdruckstoff* is of great interest.

Adrenocorticogenic Factors. The adrenal cortex also can be stimulated to discharge by sympathetic nerves, either through production of adrenocorticotropic hormone from the pituitary[30] or directly via sympathetic nerve endings in the medulla.[31] A pressor mechanism which appears to act principally in hypertension is probably mediated by the adrenal cortex. Hypertension is common in adrenal cortical hyperfunction and this fact has led to a considerable amount of investigation on the role of this organ. Only a few facts are

* $\phi\acute{\epsilon}\rho\omega$ = hold up; $\tilde{\epsilon}\gamma\tau\alpha\sigma\iota\varsigma$ = pressure. The name was suggested by Henry A. Schroeder, Jr.

known: (1) Desoxycorticosterone acetate (DCA) injected daily raises blood pressure in hypertensive subjects.[32] The injection of this material, however, if continued loses its action on blood pressure, weight and urinary chlorides.[1,8,33] In addition, blood pressure does not rise when dietary salt is also restricted.[8] (2) DCA or desoxycorticosterone glucoside acts as a prolonged pressor substance when injected intravenously, but only in hypertensive subjects[34] (and in some dogs and rats[8]). (3) DCA probably does not act by stimulating a renal pressor mechanism. Dogs who respond to its intravenous injection by hypertension respond equally well after their kidneys have been removed. Renal plasma flow and glomerular filtration rate in patients are not altered during the pressor response in the direction of efferent arteriolar constriction.[35] (4) Certain hypertensive patients maintain blood pressure levels which are high when the intake of salt is high and low when it is restricted. Blood pressure of these individuals is apt to be sensitive to DCA or DCG, a very prolonged effect following a single injection.[36] We have been unable to isolate pherentasin from their blood by methods giving results in other cases. It is probable that patients of this variety exhibit a different pathogenesis, as will be discussed later, for the sodium and chloride content of their sweat is low.*

Effects of These Pressor Mechanisms on Various Vascular Beds. Stimulation of sympathetic nerves leads to increased peripheral resistance especially of the splanchnic bed. The relative resistances of various local circulations in chronic hypertension have not been thoroughly studied and therefore little is known regarding the distribution of the effective peripheral resistance. This is an important question for its solution may give a clue to the identity of the *Hochdruckstoff* and to the relative part played by neurogenic and humoral mechanisms. Pickering[37] and Prinzmetal and Wilson[38] believed that humoral mechanisms acted to an approximately equal degree on all arterioles throughout the body. Others, notably Sheard,[39] Abramson[40] and Stewart et al.[41] produced indirect evidence that certain areas might be more affected by vasoconstriction than others; these differences were altered by sympathectomy.[42] To generalize from experiments made on the assumption that a single mechanism operates to elevate blood pressure is probably erroneous. In certain cases the neurogenic element predominates, in others one or more humoral ones. It is necessary, therefore, to know as exactly as possible where the resistance lies—in the splanchnic bed predominantly, in all beds equally, or in intermittent variations between them. By the use of a photoelectric rectovaginal plethysmograph, marked lability of an area of the splanchnic bed in some hypertensive women has been demonstrated.[8]

Studies have principally concerned themselves with the renal vascular bed. Efferent arteriolar constriction measured by clearance technics is uniformly present in chronic sustained hypertension but may be absent during early stages.[43] The conditions of the experimental procedure and the fluctuating nature of early hypertension, which usually contains a large neurogenic component, do not lend themselves to exact determinations of renal blood flow during the stresses of daily living. Therefore, the most that can be said is that *at rest* early hypertensives do not show renal vasoconstriction while well established ones do.

EFFECTS OF HYPERTENSION ON THE VASCULAR SYSTEM

The presence of prolonged arterial hypertension leads to changes in the arterioles throughout the body but more especially in those of the kidneys. This view is at variance with that of Goldblatt[19] who believes that afferent renal arteriolar disease may come first and cause hypertension by producing renal ischemia. Evidence for the secondary

* There is little direct evidence that the adrenal cortex is in a hyperactive state in most individuals with hypertension. The urinary excretion of corticoids and 17-ketosteroids is not disturbed, there is no alteration in sensitivity of blood sugar to insulin;[36a] and the salt concentration of sweat is normal. A well defined group, however, does show abnormalities (vide infra).

nature of arteriolar disease is increasing. Renal biopsy studies on man have shown none to minimal renal vascular disease in 46 per cent of 500 hypertensive patients.[44] The argument that the small size of the renal biopsy did not give a true picture of the whole kidney is not valid; bilateral biopsies were similar; few pathologists study more than one good section of kidney, and the consistency of the findings strongly suggested that a representative sample was obtained. Various unilateral renal affections in rats caused chronic hypertension with vascular disease, even arteriolar necrosis, in the opposite kidney.[45,46] Because dogs usually require constriction of *both* renal arteries to maintain hypertension, the experimental approach is difficult; however, in this laboratory by using special technics and choosing nervous, high-strung animals, we have produced hypertension which has slowly caused some arteriolar changes in a contralateral kidney;[35] these studies are continuing. Unilateral renal affections with hypertension in man are associated with arteriolar disease in the opposite kidney. Removal of a unilateral ischemic kidney in the rabbit does not "cure" the hypertension caused by the ischemia.[47] Therefore, in the rat, man and probably the dog arteriolar nephrosclerosis appears to be the result of, and not the cause of hypertension, although it must, by the very nature of the lesion, act to maintain renal ischemia and therefore contribute to an already elevated blood pressure.

There is further suggestive evidence that hypertension damages arterioles. The kidney of the dog on which there is a Goldblatt clamp is "protected" against vascular disease.[48] Chronic pulmonary hypertension resulting from long-standing mitral stenosis or pulmonary emphysema is accompanied by pulmonary arteriolar—and arterial—lesions similar to those seen in peripheral hypertension. If lesions accompany hypertension in either the greater or the lesser circulation, are confined to that circulation and do not uniformly occur in its absence, the evidence becomes more than suggestive that high arterial pressure can cause vascular disease. In benign arteriolar sclerosis we can assume that the lesions are those secondary to chronic strain and overwork, until proof is offered that the *Hochdruckstoff* causes changes in blood vessels. Strain may also predispose larger vessels to arteriosclerosis if the metabolic changes necessary for its development have occurred. The necrotizing lesions seen in the malignant stage of hypertension may be the result of toxic substances released by severely ischemic kidneys; experiments in dogs suggest that this may be so.[49]

The Vicious Circle of Arteriolar Disease, Renal Ischemia and Hypertension. When hypertension has become well established through the mechanisms described previously and arteriolar nephrosclerosis has appeared as a result, the renal vascular changes themselves cause renal ischemia.* Superimposed on this "fixed" renal ischemia of disease is the intermittent renal ischemia of neurogenic vasoconstriction. When the latter is abolished or modified by surgical or chemical[13] sympathectomy, or by adequate rest, sedation and psychotherapy,[7] a "floor" is reached; the level of blood pressure of this "floor" is probably maintained principally by humoral vasoconstrictor substances, with possibly a small contributing element due to organic arteriolar narrowing in the periphery. Therefore, complete reversal of the elevated blood pressure to normal levels by any means can occur only in the earlier

* While actually meaning a lowered flow of blood through the kidneys, the term renal ischemia as used in this discussion also includes situations in which ischemia is potential; that is, absent or of minor degree when the head of arterial pressure is high but present when it is low. Structural changes in renal arterioles or arteries, for example, will lead to such a condition. The assumption is therefore made that renal resistance to blood flow is increased, that this increase leads to ischemia, that ischemia leads to the formation of nephrogenic pressor substances and therefore to a higher peripheral pressure which partly compensates, and that compensation leads to the establishment of the pressure-flow relationships of the kidney at a different level. For this level to be maintained we can assume that intermittent ischemia (or hypoxia) occurs in which flow is reduced below renal needs or requirements, and which recalls into action these regulative mechanisms for peripheral pressure.

stages which are associated with little or no organic renal vascular damage.

The superimposition of neurogenic vasoconstriction on organic, with intermittent episodes of greater degrees of renal ischemia, leads to the intermittent production of more rapidly descending spiral, renal ischemia becoming "decompensated" in spite of higher blood pressure. Signs of acute vascular damage in the ocular fundi, progressive renal insufficiency and death from uremia characterize this "malignant stage" of

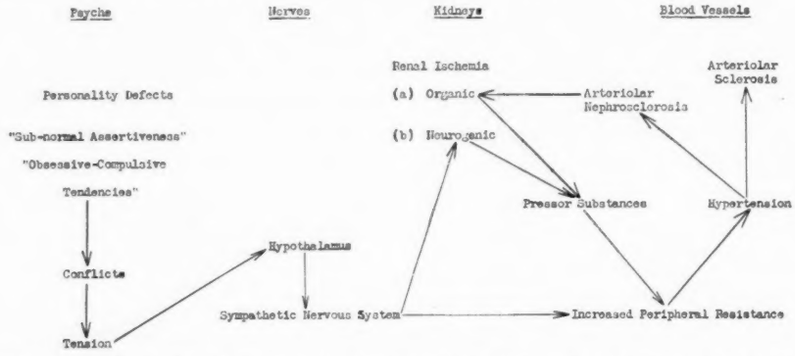

FIG. 1. Pathogenesis of neurogenic hypertension. Sequence of events leading to sustained hypertension when accessory etiologic factors are absent. Repressed emotional tension causes discharges of the sympathetic nervous system via the mid-brain leading to generalized vasoconstriction. The kidneys are included in the response. The resultant disturbance of intrarenal hemodynamics leads to the production of pressor substances. The replacement of humoral for neurogenic vasoconstriction sustains the hypertension for longer periods of time. Repeated discharges eventually lead to sustained hypertension which in turn causes changes in the walls of the arterioles, especially those of the kidneys. The organic renal ischemia caused thereby promotes a vicious circle in which the continued production of pressor substances is predominant. The neurogenic element is superimposed thereon.

Hochdruckstoff; the resulting higher arterial pressure gradually leads to greater degrees of nephrosclerosis, and the nephrogenic "floor" becomes fixed at higher and higher levels. After varying periods of time some organ gives way to the constant strain and an accident occurs. It is not within the province of this discussion to describe the secondary damage to heart and brain. The cardiac hypertrophy is probably the result of overwork, and cardiac accidents secondary to overstrain or to coronary arterial diseases. Cerebral blood vessels rupture from strain on areas weakened by associated vascular disease or abnormalities because of the relative thinness of their adventitia.[50] Renal insufficiency supervenes on three accounts: first, because (for unknown reasons) the nephrosclerosis progresses rapidly; second, because accessory renal parenchymal diseases are present; and third, because in some way, possibly through outside influences, this vicious circle becomes a hypertension, which sometimes may be variable in its course and occasionally is reversible.

PROBABLE PATHOGENESIS

Therefore, the pathogenesis of hypertension can be considered somewhat according to the following: Nervous stimili arising in the brain from emotional tensions are discharged via the hypothalamus and the sympathetic nervous system. The diathesis which produces this type of discharge may be hereditary or developmental. As these discharges occur they produce generalized neurogenic vasoconstriction which includes the kidneys. Vasoconstriction in the kidneys results in the formation of blood-borne pressor substances which serve to maintain the elevated blood pressure. The results of such an emotional discharge in predisposed individuals may persist for some length of time, perhaps a matter of hours. Subsequent repetitive discharges result in

establishment of the pattern of reaction, each period of renal vasoconstriction producing pressor substances. Eventually these pressor substances themselves cause changes in the architecture of the renal arteriolar bed which by their very nature result in organic renal ischemia. Thus hypertension which at first was intermittent becomes constant. (Fig. 1.) It is probable that almost all patients with hypertension not secondary to other diseases demonstrate to a greater or lesser extent this pattern of reaction. When the extent is considerable, "neurogenic" or "psychoneurogenic" hypertension is the result. The various influences causing these changes can be modified by accessory conditions or diseases affecting the several organs or systems involved. The "vicious circle" of renal ischemia → pressor substances → hypertension → renal arteriolar sclerosis therefore can be initiated by disturbances in intermediate pathways as well as of the whole pathogenetic mechanism.

CLINICAL TYPES OF HYPERTENSION DEPENDENT ON ACCESSORY ETIOLOGIC FACTORS

Up to this point we have described the psychic and neurogenic aspects of arterial hypertension and its organic consequences. Other factors organic in nature can contribute to hypertension in addition to the nervous. These are: parenchymal disease of one or both kidneys, arteriosclerosis with narrowing of one or both renal arteries at their mouths or along their courses extra- and intrarenally, and disturbances of the endocrine glands, especially of the adrenal cortex. When accessory diseases are absent, usually the condition is pure "neurogenic" hypertension. When accessory conditions are present in addition to the psychoneurogenic, it appears preferable so to designate cases suffering from them, since course, prognosis and therapy may be quite different. While differential diagnosis between the various types may be difficult if not impossible when one examines a short segment of the course of the disease without a thorough knowledge of the patient's history, well documented cases usually can be classified by clinicians with experience and understanding. A brief description of the points of differentiation of "pure" cases may be helpful although many are "mixed."

Renal Hypertension. While the nephrogenic factor probably operates in most cases of hypertension this term is used to designate those with renal parenchymal disease, including pyelonephritis, glomerulonephritis "masked" by hypertension, chronic urinary obstruction, calculi, etc., which are unsuspected until searched for thoroughly or the signs of which become less evident as nephrosclerosis advances, hypertension being the presenting condition. The urologic disease is probably the initiating factor. This view is at variance with that of Smith[51] who believes that there is little evidence that the kidneys play a primary or initiating role since removal of one diseased kidney rarely "cures" the hypertension. When one accepts the concept, however, that arteriolar nephrosclerosis is the *result* of hypertension and can maintain renal ischemia and hypertension even when its causes are removed, the view that urologic disease may initiate hypertension in susceptible individuals becomes more tenable. When urologic disease is unilateral, failure of nephrectomy to lower the blood pressure therefore is explained by the presence of secondary contralateral arteriolar nephrosclerosis; favorable results can be expected in those relatively rare instances when arteriolar disease in the opposite kidney is minor or absent.

In a recent excellent review Smith[3] listed only forty-seven cases of hypertension associated with urologic diseases apparently "cured" by nephrectomy, commenting on the relative rarity of proven renal hypertension. It is interesting that the average age of these patients was just over twenty-seven years, that all but ten were under forty, and nineteen were under twenty when nephrectomy was performed, a relatively young group for advanced hypertension. To these can be added two cases of our own, previously reported,[52] who have normal blood pressures more than ten years after nephrec-

tomy. If unilateral urologic or renal affections can cause hypertension in man, as it can in rats,[53] goats,[54] rabbits[55] and certain dogs,[35] and if hypertension itself can cause renal arteriolar sclerosis, as it does in rats, and probably in dogs and man, an explanation is offered for the apparent discrepancy in results. Furthermore, if unilateral disease can give rise to hypertension there is no reason to believe that bilateral disease will not; the experimental evidence is clear on this point.

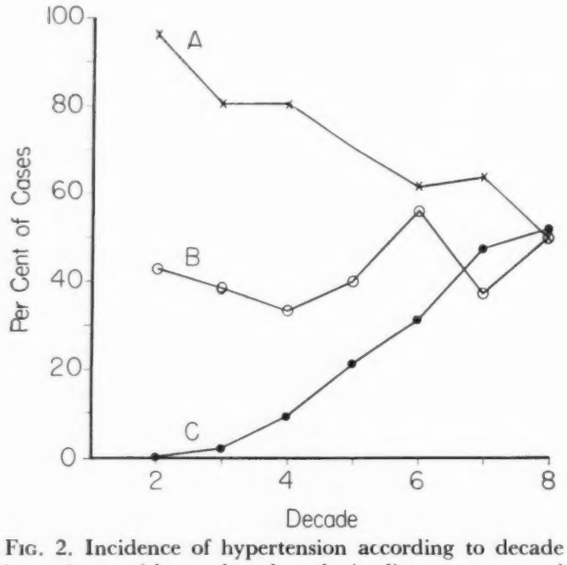

FIG. 2. Incidence of hypertension according to decade in patients with renal and urologic diseases compared with incidence in the general population. A, with renal excretory insufficiency (280 cases); B, without nitrogen retention (seventy-one cases); figures taken from Bell's[56] and Addis'[57] tables. C, incidence in general population (1,981 cases) averaged from Friedman et al. and Braasch et al., quoted by Smith.[3] Although the series is small, the incidence in renal disease is approximately as high in the younger age groups as in the older, and much greater than that of the general population.

Smith has clearly demonstrated that arterial hypertension is little more common when organic renal disease is present than when it is not. Bell[56] intimates that he has come to the same conclusion. Analysis of his cases and those of Addis[57]—1,047 patients with various types of organic renal disease—indicates that diastolic pressures of 90 or more were present in 52.9 per cent, which is little greater than the incidence for the general population. When patients probably or certainly exhibiting nitrogen retention were excluded, both with normal and with high blood pressures (745 cases), 43.4 per cent had hypertension. (Fig. 2.) There are two differences, however, which appeared from these statistics. First, the age incidence of hypertension in renal diseases was lower, many severe cases occurring in childhood. Second, the course of the disease was usually shorter than that commonly seen in "essential" hypertension. To deny that renal diseases can be contributory to hypertension in man is to oppose the weight of voluminous experimental, clinical and pathologic experience. When definite experimental mechanisms have been evoked, and in part understood, the burden of proof must be placed on those who insist that these mechanisms have little if any clinical counterpart.

It is not surprising that the incidence of hypertension in urologic diseases is not much greater than in the general population; a situation such as this could be expected if both the predisposition or diathesis and the urologic disease were necessary to cause hypertension. Such seems to be suggested by the fact that urologic and renal disease occur both with and without hypertension; two factors must therefore be at work. However, when both occur together the hypertension is apt to (1) be more severe, (2) begin earlier and (3) terminate earlier in renal failure. The clinical characteristics of a group of eighty cases of hypertension associated with previously unsuspected organic renal and urologic diseases[58] were: (1) 64 per cent had a history of hypertension in their families; (2) the average duration of the disease from known onset to death was 6.9 years in males and 9.0 in females, or 7.4 years for the whole group; (3) the shortest duration was six months; (4) retinitis, that is, hemorrhages, exudates or papilledema, was present in 48 per cent; (5) a malignant course was common (21 per cent); (6) death from renal or renal and cardiac failure occurred in 68 per cent; (7) the diastolic pressure was often very high and appeared to be "fixed." These findings contrast with those of other observers

analyzing groups of hypertensive patients without attempt at classification, a malignant course being rare (1.3 to 5 per cent), renal failure accounting for about 5 per cent of deaths and exudative retinitis being present in 1 to 19 per cent.[59,60] On clinical grounds, therefore, it appears that when the constitutional or psychoneurogenic factor is present, and the patient develops organic renal disease, the result not infrequently may lead to severe hypertension with a tendency to develop renal insufficiency. When the former is absent, hypertension occurs possibly only with renal excretory insufficiency.

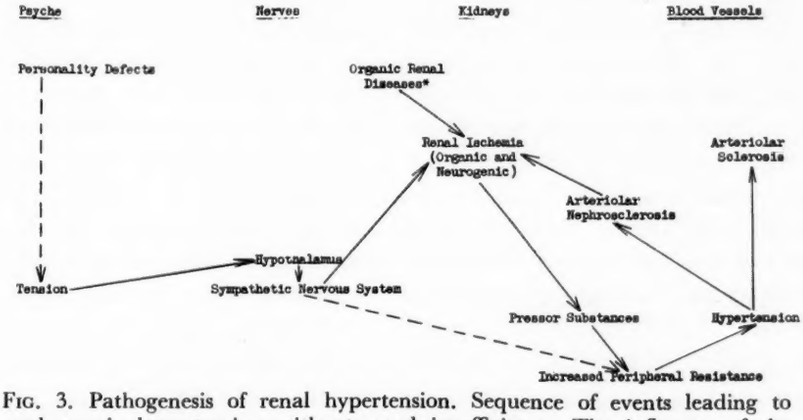

FIG. 3. Pathogenesis of renal hypertension. Sequence of events leading to nephrogenic hypertension without renal insufficiency. The influence of the psychoneurogenic factor may be of variable magnitude but is superimposed upon intrinsic changes in the circulation of the kidney produced by renal and urologic diseases. Humoral vasoconstrictor substances are formed as a result of the action of these two influences and the vicious circle is established. When arteriosclerosis obstructs partially the renal arteriolar tree, the sequence of events is similar except that less nephrosclerosis will result.

It is conceivable that moderate renal ischemia caused by organic processes may become severe through added neurogenic vasoconstrictor influences. Experiments in anesthetized dogs conclusively show that this is so although the point has not been demonstrated in man. Epinephrine reduces renal blood flow in the dog only momentarily. However, when renal hemodynamics are previously altered by an adjustable clamp on the renal artery, the action of epinephrine on blood flow is greatly enhanced. Under these conditions one-hundredth the dose will cause renal ischemia lasting ten times as long.[61] If the implications of these observations can be carried to man, summation of the effects of moderate renal ischemia and moderate neurogenic stimulation may affect renal blood flow profoundly. (Fig. 3.) Experiments done in this laboratory, however, have shown that the subcutaneous injection of 0.5 mg. of epinephrine reduced effective renal plasma flow, as measured by the clearance of para-amino hippurate, to a level 71 per cent of the control values in three normotensive subjects and to a level of 66 per cent of control values in three hypertensive patients. The difference is not striking and the duration of action was similar (up to fifty minutes).

Neurogenic Hypertension. As opposed to the renal type, pure neurogenic hypertension has shown the following characteristics: (1) psychologic disturbances of more obvious nature; (2) fluctuating blood pressure even after years of apparently sustained hypertension, with a good response to sedation and sympathicolytic or blocking agents (a lower nephrogenic "floor"); (3) little evidence of cardiac or renal damage; (4) the presence of the "hypertensive diencephalic syndrome," with reproduction of attacks by intradermal histamine;[12] (5) evidences of vasomotor disturbances in symptoms and signs, such as palpitation, tachycardia, cold, clammy extremities especially during emo-

tional stress; (6) a prolonged benign course; (7) slight diurnal variations in body temperature to febrile levels; (8) absence of accessory etiologic factors such as primary renal diseases, specific endocrine disturbances and little or no arteriosclerosis; (9) marked fluctuations of blood pressure occurring spontaneously and with respiration when measured by direct methods. The "histamine test" for producing the diencephalic blush and the response of the blood pressure to the intravenous injection of tetraethylammonium ion have been found most useful in differentiation.* In 62 per cent of a group of forty-six such patients studied, headache was the most distressing symptom. Retinitis was rare. The condition occurred more often in females (84 per cent).[62] While the diagnosis of neurogenic hypertension is made partly by exclusion, the aforementioned characteristics occur with less frequency and predominance in the renal type. The easy flushing of such patients when embarrassed or under the strain of an interview often suggests this condition.

Endocrine Hypertension. Of readily discernible nature is the so-called endocrine type of hypertension in which glandular disturbances are believed to predominate. While the adrenal cortex may be stimulated by activity of the sympathetic nervous system, on clinical grounds certain patients appear to be suffering from some form of intrinsic overactivity. Others have as yet undescribed endocrine diseases manifested by certain clinical findings.

Two definite groups can be described; one of which has been called pseudo-Cushing's syndrome,[63,64] the other going by the cumbersome name of "non-goitrous thyrotoxic hypertension," both seen principally in women. The former syndrome is characterized by the presence of obesity of the trunk, thighs and upper arms, which usually develops rapidly, often after some physiologic endocrine disturbance (puberty, pregnancy menopause) or an operative procedure (hysterectomy, oophorectomy); it is not uncommon after the third or fourth pregnancy. The central obesity is usually less well developed than that seen in Cushing's syndrome; the rapidity of onset is noteworthy, patients often gaining 30 to 50 pounds within a year. Irregularities of menstruation are almost universal. The hypertension varies from mild to severe but is accompanied by little if any renal damage. Albuminuria is usually absent or of slight degree, but retinitis has been noticed in a number of cases, disappearing readily during treatment. Other signs and symptoms commonly but not universally encountered are: pale striae on thighs and sometimes arms, a "buffalo" type of hump on the back, tendency to easy bruising and ecchymoses, hirsutism, mottled cyanosis of extremities especially of legs, abnormal glucose metabolism with diabetic types of glucose tolerance determinations or mild diabetes which may regress spontaneously, hyperchloremia, excessive sensitivity of the blood pressure to injections of desoxycorticosterone and of the blood sugar to insulin, low excretion of 17-ketosteroids, cyclic disturbances of water metabolism with long periods of oliguria, and a dislike of salty foods. These patients lose weight with considerable difficulty on low caloric diets under controlled hospital conditions. The sodium and chloride concentrations of their sweat is always low.[65] Of great clinical interest is the response of the hypertension and its manifestations to dietary restriction of salt (and calories). Dramatic response of the blood pressure, retinitis and symptoms may follow severe limitation of dietary salt; when salt is added to the diet, blood pressure rapidly rises. Clinical differentiation is therefore important, carrying with it therapeutic implications. The cardinal signs are central obesity, menstrual disturbances and the low level of sodium and chloride in sweat. This last finding strongly suggests overactivity of the salt-retaining hormone of the adrenal cortex.[65a] Post-

* The intradermal injection of histamine does not usually produce the blotchy, mottled blush so characteristic of neurogenic hypertension in subjects with other types. The "TEA floor," however, may occasionally be low in endocrine and arteriosclerotic types, even when the malignant stage has begun.

mortem findings have been scanty as the disease is benign, but in two cases the adrenal cortex was hyperplastic, a lesion not wholly unexpected.* (Fig. 4.)

"Non-goitrous thyrotoxic hypertension" is a condition described in the earlier literature[67] characterized by severe hypertension often ending in the malignant phase, a continuously elevated basal metabolic rate which does not respond to thyroidectomy or iodine, the fairly frequent presence of the diencephalic syndrome,[62] severe symptoms especially of headache and a relatively rapid course. Pathogenesis has not been defined.

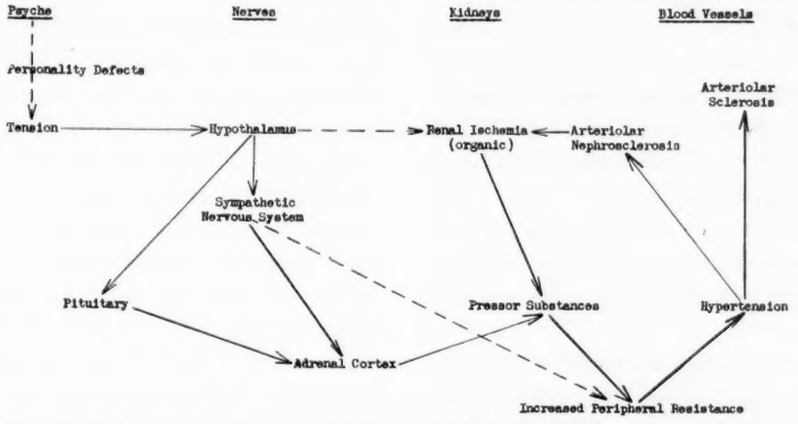

FIG. 4. Pathogenesis of endocrine hypertension. Possible sequence of events leading to endocrine hypertension. The role of the psychoneurogenic factor is not clearly established but may in some way influence the adrenal cortex to hyperactivity. Adrenal cortical hormones may themselves act as pressor substances but are probably not specific renal vasoconstrictors. The resultant hypertension leads to only moderate degrees of arteriolar nephrosclerosis and the institution of the vicious circle of renal ischemia → pressor substances → hypertension.

Hypertension Associated with Arteriosclerosis. The theory that diastolic hypertension is dependent on generalized arteriosclerosis is the least proven of the various hypotheses. When generalized arteriosclerosis occurs during later years, systolic pressure rises because of diminished vascular elasticity and diastolic pressure falls slightly. With this condition we are not concerned. The processes which cause diastolic hypertension may be construed theoretically as follows: When the psychoneurogenic factor is present to a slight degree (and a relatively slight degree must be postulated or neurogenic hypertension would have developed at an earlier age) little effect on blood pressure might be expected. If arteriosclerosis is located, however, in such a place as to interfere moderately with blood flow through the kidneys by obstruction of the orifices, lengths or intrarenal branches of the renal arteries, the combined action of both influences results in hypertension. Blackman's observations on the frequency of renal arterial narrowing from arteriosclerosis are worthy of consideration.[68] The aging process in the kidney probably does not contribute to this condition, for a gradual reduction in the number of nephrons, not a change in their internal anatomy, is most frequently seen in older normotensive individuals.[69]

We are therefore in agreement with Goldblatt that "the possible contribution of this

* In a recent review Findley[66] discussed the work of Heinbecker and others, and advanced the theory that hypertension is due to hypofunction of the neurohypophysis, which acts upon other endocrine organs leading eventually to a state of increased tissue sensitivity to the action of various pressor substances. As is evident, we do not agree that this hypothesis applies to the vast majority of cases of hypertension. It is possible, however, that some mechanism such as this may be concerned with the cases discussed here, and which probably account for 20 per cent of all hypertensive women. If the sodium and chloride content of sweat may be considered as an index of adrenal cortical hyperfunction, there is no evidence of hyperfunction in the usual case of renal or neurogenic hypertension. Proof of this hypothesis awaits pathologic demonstration of pituitary changes in hypertensive patients, and experimental production of hypertension in animals by reproducing these changes.

obliterative sclerosis of the large intrarenal arteries, and even of the main extra-renal artery, to the disturbance of intra-renal hemodynamics has been underestimated."[70] When such a large supply of blood (500 to 600 cc. per minute) is going to a kidney through an artery (which never appears large enough) at a low resistance, it is obvious that minor stenosis of the artery would cause relatively profound peripheral changes. Experiments conducted with models and isolated limbs of dogs have demonstrated this to be hemodynamically so.*[71] By strict definition this type of case should be included in the group designated renal hypertension; they are separated because of their vascular aspect.

Clinically these cases can be differentiated by certain suggestive signs: the onset occurs later in life, usually in the fifth or sixth decades; the course is very variable, depending upon the degree and site of the major vascular changes, but the hypertension itself is benign and only slowly progressive; retinitis is unusual; renal insufficiency is rare, death usually resulting from stroke or cardiac accident or failure; and severe symptoms referable to hypertension itself are unusual. The slowly progressive course can be explained by the nature of the lesions themselves and the relatively small part played by the neurogenic component. While comprising the most common type of hypertension, diagnosis can be made only by exclusion and by the presence of generalized arteriosclerosis.

* Either flow or pressure beyond a constriction is reduced, depending upon whether arteriolar constriction or dilatation occurs. Normally the kidney has a low resistance to flow. The resistance beyond a Goldblatt clamp in dogs' kidneys, however, is increased, indicating renal vasoconstriction.[71] Therefore, the resistance offered by the arterial constriction is associated with high resistance in the arteriolar bed. Obviously, if renal arterial constriction causes renal arteriolar constriction, blood flow must fall to even lower levels than those resulting from the obstruction in the artery alone. As far as is known, the renal changes distal to a Goldblatt clamp are the following: increased vascular resistance, varying degrees of cortical hypoxia, acidification of the periphery of the cortex,[71a] possibly disturbances of electrolyte excretion and enzymatic constitution, and diminution of mean and possibly pulse pressure.

SECONDARY HYPERTENSION

Hypertension secondary to known pathologic conditions also can be caused by disturbances of four main systems: renal, nervous, endocrine and renal vascular.[62] We do not intend to discuss these diseases at length. They fall into two general classes, those in which hypertension is associated and develops with renal excretory insufficiency, and those in which it does not. Among the latter renal failure sometimes supervenes. Elevated blood pressure accompanies renal insufficiency in more than two-thirds of cases (71.4 per cent of Bell's series) being more common in younger people. (Fig. 2.) The reason for the absence of hypertension in a large number of patients with renal insufficiency is not known. For example, it is absent in 38 per cent with polycystic disease, 50 per cent with urinary obstruction, and 30 per cent with glomerulonephritis. Its frequency suggests a causal relationship with the renal disturbance but this is not invariably so.

Careful analysis of cases of coarctation of the aorta indicates that true diastolic hypertension does not usually accompany the abnormality. In one series it was present in only five of twenty cases when blood pressure was measured directly in the femoral artery.[72] It appeared to develop or become worse in one-third of another series[73] and did not completely disappear after the aortic defect was repaired.[35] These observations suggest that some patients have coarctation of the aorta alone (with often a systolic elevation above the constriction) while others have coarctation plus hypertension (with a diastolic elevation below the constriction). Although the series is small, the possibility exists that chance occurrence of the hypertensive diathesis and coarctation is responsible for these discrepancies. The degree of coarctation did not correlate in these few subjects with the degree of true hypertension.

A similar argument may be valid for the explanation of the hypertension secondary to other diseases, notably renal. The large proportion of cases without hypertension

but with renal diseases believed to be associated with it suggest that two factors again may be operating, the combination of which results in elevation of blood pressure. In some conditions both factors may be renal, as suggested by Bell, but in most the evidence indicates that the hypertensive diathesis, mild, moderate or severe, acts in conjunction with a renal factor. Any other explanation is inconsistent with the facts. When Cushing's syndrome and other endocrine diseases are examined from the same point of view, one is forced to the same conclusion, for hypertension is absent in a fair proportion. Data are not available to suggest whether hypertension is the result of two interacting influences, neurogenic and adrenal. The occasional absence of hypertension in this condition can also be explained by the interrelationships of the actions of the various adrenal cortical hormones which may be present in excessive amounts.

Pheochromocytomas produce intermittent hypertension which can lead to sustained hypertension. As far as is known, epinephrine and nor-adrenalin are the causative agents,[74] and the condition is curable by surgery. And yet the same pathologic findings may be present in the kidneys of patients with long-standing pheochromocytoma as in those with long-standing neurogenic hypertension. Pathogenesis in this case follows a similar pattern. Although the psychogenic factor may be absent, the neurogenic one as exemplified by its chemical effector substances is strong.

Chronic glomerulonephritis without nitrogen retention may exist with or without hypertension. When hypertension is present it may be severe and in certain stages indistinguishable from that called "essential." Only at the beginning and end of the disease can a differential diagnosis be made, often only by necropsy. We can postulate therefore the interaction of the two factors to produce hypertension, the psychoneuroaenic and the renal. When the former is gbsent, hypertension in chronic nephritis occurs with renal excretory insufficiency, possibly the result of retention of some pressor substance. The same may be true for polycystic disease of the kidneys in which hypertension is frequent but not universal. The pressor substance is probably not related to guanidine, phenol or creatinine.[75]

COMMENT

When the four types of hypertension are considered as separate conditions having in common only two components, the psychoneurogenic factor in degrees from mild to severe and increased peripheral resistance, differentiation is not too difficult. It is important from both prognostic and therapeutic viewpoints. The analysis of any procedure designed to test or alter hemodynamics must be made in the light of the conception that "essential" hypertension is not a single disease, just as diabetes is not. Much of the confusion in the literature on pathology, physiology and response to therapeutic measures is probably caused by the tendency to regard hypertension as having a single pathogenesis. The present disagreement as to the relative importance of either renal, neurogenic or adrenal pressor mechanisms is the result of this tendency. While there is general agreement that blood pressure can be elevated by many mechanisms, one is often considered implicated to the exclusion of others, in spite of the fact that hypertension is only a sign, analogous to fever, tachycardia, albuminuria or hyperglycemia.

Therapy, as in all conditions, must be directed against cause. The common factor appears to be psychoneurogenic. The relative weight of the factor varies from case to case except in neurogenic hypertension, and therefore the most successful psychotherapy can be expected to produce variable results. Psychotherapy is meant to include all measures which tend to relieve anxiety and tension and cause the patient to turn his welfare and his worries over to someone else. Religious or quasi-religious faiths, limitation of activities, strict regimens, dependency on non-specific drugs, severe operative procedures, prolonged hospitalization and

frequent clinic or office visits come under this category and are of effect in some cases. Any therapeutic procedure vigorously pursued by both physician and patient will show results in more moderate cases. Psychotherapy has sometimes altered the course of hypertension when used in the earliest stages. Psychotherapy can attempt to re-educate the individual so that he will react to his conflicts by overt action or by insight and logic and not resolve them by repression, emotional tension and subsequent discharge via his hypothalamus and his sympathetic nervous system. The deficiencies of personality, however, are so deeply ingrained and fundamental to the individual that intense psychotherapy of the wrong kind may make the situation worse.

The neurogenic factor, the effector mechanism of the psychic discharges, can be altered in two ways other than by changing its psychic cause. The newer sympatholytic agents are now used only for brief experiments to evaluate the degree of sympathetic activity. Their action often calls out reactions attributable to parasympathetic activity. So far they have been relatively ineffective for continued use. A drug specific for the neurogenic factor must be taken continuously, produce a sustained "chemical sympathectomy," should probably block the action of nor-epinephrine, and preferably should be active by mouth. When such a drug is developed, it will be useful in cases having predominantly neurogenic hypertension without severe arteriolar disease of the kidneys. Evidence for the reversibility of advanced arteriolar disease by sympathectomy is not available.

The other method is by extensive sympathectomy which has proven valuable in only a certain proportion of cases (10 to 20 per cent),[76] although it does seem to alter the malignant phase into one more benign. The apparent failures of this method are explicable on four grounds: (1) If arteriolar disease is severe, removal of the neurogenic component will not result in the abolition of renal ischemia. (2) The neurogenic component is very variable from patient to patient. (3) Removal of nerves is incomplete. (4) Sympathetic nerves regenerate.[77] We have seen one such example: a twenty-eight year old woman whose lumbar sympathetic chain and splanchnic nerves were removed in 1946, with temporary lowering of blood pressure. Two years later lumbodorsal sympathectomy was performed; the splanchnic nerves and lumbar chain had completely regenerated, even to the regrowth of distorted ganglia. The second procedure resulted in a normal blood pressure for at least two years. The inadequacy of limited denervation of the kidneys and splanchnic bed has been stressed by Smithwick.[78] The innervation of splanchnic nerves and kidneys is very variable.

The other factor which must be controlled is humoral. Five approaches are possible: (1) destruction of the pressor material by enhancement of natural destructive agents or by artificial antagonists;[80] (2) inhibition of its formation by enhancement of natural inhibitory processes; (3) "flooding" a system with a non-toxic competitive agent;* (4) increasing the concentration of a naturally occurring antagonist; (5) increasing renal blood flow by non-specific methods, thereby lessening the production of pressor substances.[79] Identification of the pressor material is necessary before intelligent investigation can proceed along these lines. The problem is biochemical. Unless it turns out that the chemical mediators of both neurogenic and humoral vasoconstriction are identical, it is probable that both approaches will be necessary to control hypertension. There is already evidence that some patients do better when several therapeutic methods are applied together.

* It is interesting, in this respect, that the pressor effects of iso-amyl amine in hypertensive rats is about one-half as strong as in normal rats; this pressor amine, which is relatively weak, usually lowers blood pressure in hypertensive human beings, although raising it in normal subjects.[80a] Furthermore, thiocyanate ion has been found to act on renal tissue *in vivo* by inhibiting decarboxylation of those amino acids, the amines of which are pressor.[80b] Conceivably, the hypotensive action of this drug in man could be due to its ability to inhibit the formation of pressor amines from amino acids.

Advances along these lines are encouraging enough at present to justify considerable optimism for the near future. When the solution finally appears, it may be a relatively simple one. There are no grounds for the pessimistic attitude expressed by a number of workers in this field.

SUMMARY

Experimental and clinical observations on arterial hypertension are consistent with the theory that: (1) Repressed psychic disturbances of a more or less specific nature lead to increased activity of the sympathetic nervous system; (2) sympathetic stimulation may raise blood pressure acutely but also produces renal ischemia and stimulates the adrenal cortex to activity; (3) renal ischemia leads to the production of pressor substances and therefore hypertension; (4) hypertension itself causes arteriolar sclerosis, especially in the kidneys, resulting in more renal ischemia; (5) adrenal cortical activity can lead by itself to hypertension. When organic renal or urologic disease is also present, the hypertension may be more severe. When the predominant influence arises in the adrenal cortex, the disease presents different clinical manifestations. When arteriosclerosis causes renal ischemia, the type of disease is also different. Variations in the degree of the causative factors, i.e., psychic and neurogenic, along with the presence and severity or absence of contributory factors, i.e., renal and endocrine diseases and arteriosclerosis, account for the wide variation in the course of different patients, and in the relative efficacy or inefficacy of various methods of treatment.

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Seminars on Pulmonary Physiology

Pulmonary Gas Exchange*

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FROM the point of view of gas exchange the lung is an organ into which inspired gas and mixed venous blood are pumped, in which the gas and blood are distributed to the alveoli where, by diffusion, equilibrium with respect to carbon dioxide and oxygen is approached, and out of which expired gas and arterial blood pour forth. The processes involved thus include ventilation, circulation, distribution of gas and blood, and diffusion across the "alveolar membrane." † In the past decade refinements in technics have made possible a better understanding of the manner in which these major processes affect the concentrations of carbon dioxide and oxygen in the gas and blood of the lungs. In this paper the discussion of gas exchange will consist of a systematic presentation of relationships between the major physiologic processes and the concentrations of respiratory gases in the lungs.

"Ideal" Distribution and Diffusion. If an ideal situation existed in which the inspired gas and mixed venous blood were evenly distributed to alveoli in different parts of the lung and if equilibrium between the partial pressures of carbon dioxide and oxygen in the gas and blood then took place, the concentrations of carbon dioxide and oxygen which would exist in the gas and blood leaving all alveoli would have certain "ideal" values.[1] This situation is shown in Figure 1 in which P represents partial pressure, subscripts I, A and E indicate inspired, alveolar and expired gas, and subscripts $\bar{v}$, c and a indicate mixed venous, alveolar capillary and arterial blood.* The symbol I, used as a superscript, indicates an "ideal" value.

In Figure 2 curves representing the CO_2-O_2 exchange ratio (often referred to as the respiratory quotient) have been plotted using partial pressures of carbon dioxide and oxygen as coordinates.[1] The "ideal" values are indicated by the point of intersection of the gas and blood curves. The CO_2-O_2 exchange ratios for gas and for blood have the same value because the amount of CO_2 leaving the blood equals the amount entering the alveolar gas and the amount of O_2 leaving the alveolar gas equals the amount entering the blood. If "ideal" distribution and diffusion are assumed, the point at which the curves of CO_2-O_2 exchange ratio intersect indicates the partial pressures of O_2 and CO_2 in the gas and blood leaving all alveoli, and

$$P_A^I = P_c^I$$

The mathematical equations for the curves representing the CO_2-O_2 exchange ratios are derived as follows.

Equations† for CO_2 output and O_2 uptake:

† The term "alveolar membrane," as used in this paper, may be defined as the sum total of structures interposed between the alveolar gas and the hemoglobin molecules. These normally include the alveolar membrane itself, the capillary endothelium, the blood plasma, the red cell wall and the fluid within the red cell which separates the hemoglobin molecules. In disease, edema fluid, fibrous or collagenous tissue and various types of cellular exudate or infiltrate may also be included in the "alveolar membrane."

* These symbols conform to a system which has been agreed upon by several workers in the field of respiratory physiology.[2]

† $\dot{V}$ = volume per unit time; F = fraction of a given gas in a mixture of gases (dry); $\dot{Q}$ = volume flow of blood per unit time; C = concentration of a given gas in blood (ml. gas per ml. blood); c, used as a superscript, indicates that a correction has been applied which takes into account the change in volume of inspired gas on reaching the alveoli; $\dot{c}$, used as a subscript, refers to

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$$(1)\quad \dot{V}_{CO_2} = \dot{V}_A(F_{A_{CO_2}} - F_{I_{CO_2}}) = \dot{Q}_c(C\bar{v}_{CO_2} - C\dot{c}_{CO_2})$$

$$(2)\quad \dot{V}_{O_2} = \dot{V}_A(F^e_{I_{O_2}} - F_{A_{O_2}}) = \dot{Q}_c(C\dot{c}_{O_2} - C\bar{v}_{O_2})$$

Equations for CO_2-O_2 exchange ratio:

$$(3)\quad R = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}} = \frac{F_{A_{CO_2}} - F_{I_{CO_2}}}{F^e_{I_{O_2}} - F_{A_{O_2}}}$$

$$(4)\quad R = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}} = \frac{C\bar{v}_{CO_2} - C\dot{c}_{CO_2}}{C\dot{c}_{O_2} - C\bar{v}_{O_2}}$$

These equations are presented in short form for simplicity and to demonstrate the parallelism in the behavior of CO_2 and O_2. The complete equations are as follows:[2]

$$(1a)\ \dot{V}_{CO_2} = \dot{V}_A \frac{F_{A_{CO_2}}(1 - F_{I_{O_2}}) - F_{I_{CO_2}}(1 - F_{A_{O_2}})}{(1 - F_{I_{O_2}} - F_{I_{CO_2}})}$$

$$(2a)\ \dot{V}_{O_2} = \dot{V}_A \frac{F_{I_{O_2}}(1 - F_{A_{CO_2}}) - F_{A_{O_2}}(1 - F_{I_{CO_2}})}{(1 - F_{I_{O_2}} - F_{I_{CO_2}})}$$

$$(3a)\ R = \frac{F_{A_{CO_2}}(1 - F_{I_{O_2}}) - F_{I_{CO_2}}(1 - F_{A_{O_2}})}{F_{I_{O_2}}(1 - F_{A_{CO_2}}) - F_{A_{O_2}}(1 - F_{I_{CO_2}})}$$

When Equation 3 is plotted, a straight line results. In Figure 2 the units have been changed to partial pressure in mm. Hg by multiplying each F value by (P_B − 47) where P_B = barometric pressure and 47 = water vapor pressure at body temperature. Likewise, when Equation 4 is plotted using C_{CO_2} and C_{O_2} as coordinates, a straight line results. In this case the CO_2 and O_2 dissociation curves provide the relationship between units of concentration and partial pressure. Accordingly, if the physiologic CO_2 and O_2 dissociation curves are known, the blood R line can be transposed to a graph in which P_{CO_2} and P_{O_2} are the coordinates. (Fig. 2, blood R curve.) The point of intersection between the gas and blood R lines, which is determined graphically in Figure 2 can be calculated if equations for the O_2 and CO_2 dissociation curves are used.

Impaired Diffusion. If the inspired gas and mixed venous blood were evenly distributed to alveoli in different parts of the lung but if the partial pressures of oxygen in the alveolar gas and blood failed to reach equilibrium, a situation such as is shown in Figure 3 would exist. The cross-hatched area separating the gas stream from the blood stream represents an alveolar membrane across which the pressures of oxygen in the gas and blood fail to equilibrate. The symbols are the same as in Figure 1 except that superscript e specifies that the alveolar and capillary pressures are the "effective" rather than the "ideal" pressures.[3]

The essential relationships between the "effective" pressures in the gas and blood are shown in Figure 4. Both points have an R value equal to that of the lung as a whole. The P_{CO_2} values of the two points are essentially the same while a considerable gradient exists between the P_{O_2} values. This reflects the experimental finding that a measurable difference in P_{O_2} exists between the gas and blood phases at a low level of oxygenation such as that selected in Figure 4.

The "effective" pressures have R values equal to that of the lung as a whole because they represent the gas and blood leaving alveoli in all parts of the lung and must therefore be consistent with the gas exchange of the lung as a whole. If the impairment of diffusion is very severe, the O_2 gradient at the end of the capillaries will increase and both $P^e_{A_{O_2}}$ and $P^e_{c_{O_2}}$ will move further away from the "ideal" point, but will remain on the appropriate R lines since the CO_2 − O_2 exchange ratio for the lung as a whole remains unchanged. The "effective" pressures may be defined as the pressures which would exist in the alveolar gas and alveolar capillary blood, respectively, if the ratio of ventilation to blood flow were constant in all alveoli but if a diffusion gradient remained between the alveolar gas and the blood leaving the alveolar capillary.

The relationships shown in Figure 4

alveolar capillary blood as it leaves the alveolar capillary; R = CO_2 − O_2 exchange ratio.

between the CO_2 and the O_2 gradients at the end of the capillary serve to introduce a discussion of the major factors which account for the difference in the gradients. These factors are: the diffusion characteristics of the gas in question, the amount of gas diffusing per ml. blood and the slopes of the gas-blood dissociation curves.*

Carbon dioxide is approximately twenty-five times as diffusible as O_2 across an aqueous membrane. Therefore, in order that the same quantity of O_2 and CO_2 diffuse across the same area of membrane in the same time, the *mean* pressure gradient for O_2 must be twenty-five times as large as the *mean* gradient for CO_2.* The normal resting human subject has a P_{O_2} *mean* gradient of approximately 12 mm. Hg. Hence, if the same amount of CO_2 diffused, the P_{CO_2} *mean* gradient would be 12/25 or 0.48 mm. Hg. If the CO_2-O_2 exchange ratio were 0.8 indicating that 0.8 as much CO_2 diffused as oxygen, the P_{CO_2} *mean* gradient would be 0.8 x 0.48 or 0.38 mm. Hg. The *mean* partial pressure gradient between the alveolar gas and the blood in the alveolar capillary is

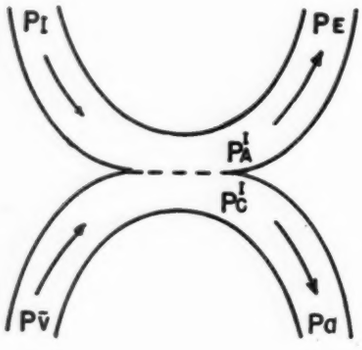

FIG. 1. "Ideal" distribution and diffusion.

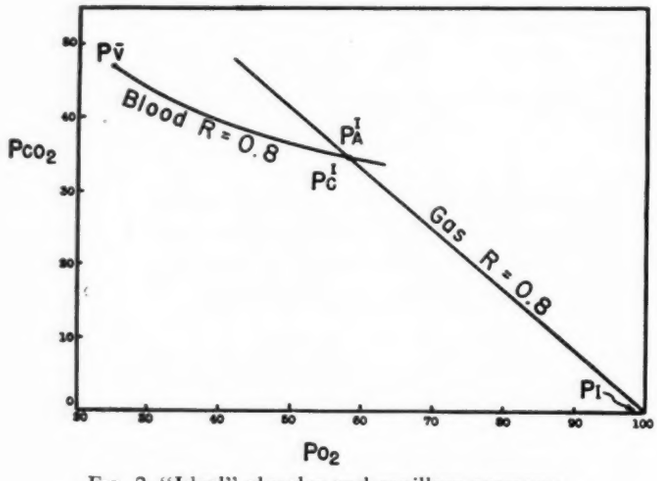

FIG. 2. "Ideal" alveolar and capillary pressures.

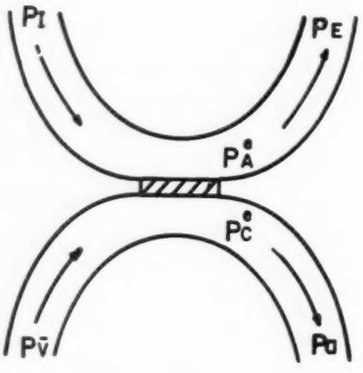

FIG. 3. Impaired diffusion.

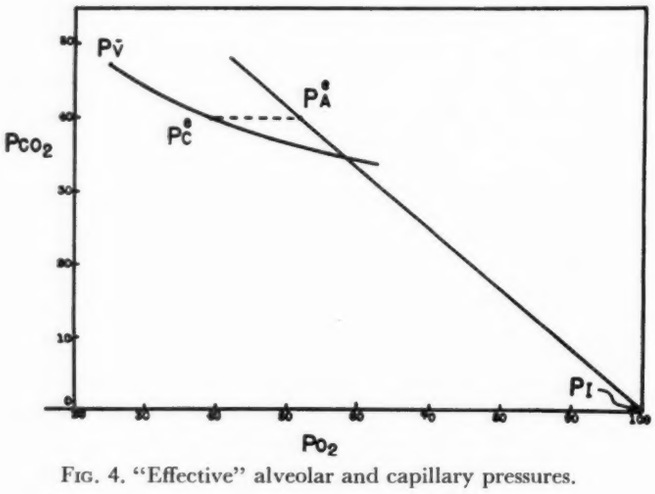

FIG. 4. "Effective" alveolar and capillary pressures.

* The diffusion characteristics of the alveolar membrane and the time available for diffusion during passage of blood through the capillary are the same for CO_2 and O_2 and hence do not account for the difference in the final gradients.

* The *mean* pressure gradient across the alveolar membrane is that gradient which, if present along the entire course of the alveolar capillary, would permit the same amount of gas to diffuse as does in fact diffuse under physiologic conditions.

thus inversely related to the diffusibility of the gas in question and directly related to the amount of gas diffusing per ml. blood.

The slope of the dissociation curve in the physiologic range is an additional factor influencing the diffusion gradient at the *end* of the alveolar capillary. If the dissociation curve is steep, the partial pressure gradient between the alveolar gas and the capillary blood changes relatively little along the course of the capillary; if the dissociation curve is flat, there is a greater change in the partial pressure gradient along the cousre of the capillary.

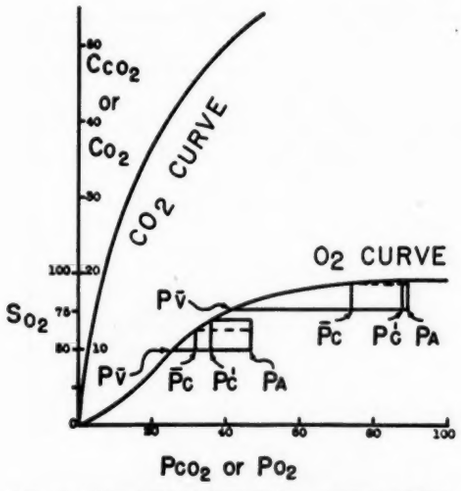

FIG. 5. Blood-gas dissociation curves; effect of slope of curve upon the diffusion gradient at the end of the capillaries. So_2 = percentage saturation with oxygen.

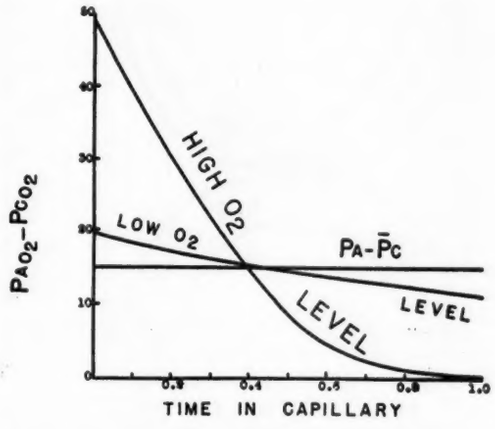

FIG. 6. Alveolar gas—capillary blood diffusion gradients along the course of the alveolar capillary at high and low levels of oxygenation. *Mean* gradient (P_A-$\bar{P}c$) same for both levels.

In Figure 5 the carbon dioxide and oxygen dissociation curves are plotted on the same scale in order to compare slopes. Even at its steepest part the oxygen dissociation curve is considerably less steep than the CO_2 curve.

The O_2 curve, although always less steep than the CO_2 curve, is steeper in its middle portion than in its upper portion. The effect of difference in slope upon the gradient at the end of the capillary therefore can be demonstrated by examining relationships at two different portions of the O_2 dissociation curve. Figure 5 has been constructed to illustrate this point. A steep segment and a relatively flat segment of the oxygen dissociation curve have been chosen to represent the conditions obtaining in a subject at two different levels of oxygenation. In each case the difference in hemoglobin saturation between the inflow and outflow ends of the capillary (the capillary-venous difference) is the same. In passing along the alveolar capillary, the P_{O_2} of the blood increases from the venous level to the end-capillary level, following a pattern defined by the dissociation curve. Values for alveolar P_{O_2} have been so chosen that the gradient between alveolar P_{O_2} and *mean* capillary P_{O_2} ($\bar{P}c_{O_2}$) is the same at both levels of oxygenation. The final gradient at the end of the capillary, $P_{A_{O_2}} - P'c_{O_2}$, is seen to be much smaller at the higher level of oxygenation where the curve is flatter than it is at the lower level of oxygenation where the curve is steeper.[4]

The rate of diffusion for any gas at each point along the course of the alveolar capillary is directly proportional to its pressure gradient existing between the alveolar gas and the capillary blood. Accordingly, a graph showing the rate of diffusion at each point also shows the manner in which the partial pressure gradient varies at each point. Figure 6 is such a graph and the rates of diffusion at both high and low levels

of oxygenation have been plotted. The time in the capillary is arbitrarily taken as unity, and equal and constant rates of blood flow at the two levels of oxygenation are assumed. The diffusibility of the oxygen is the same at each level and the *mean* alveolar-capillary gradient, both being but a fraction of a mm. Hg. When a low oxygen mixture is breathed, the final O_2 gradient becomes much larger than the CO_2 gradient. This is the condition represented in Figure 4. As will be mentioned, the variable size of the diffusion

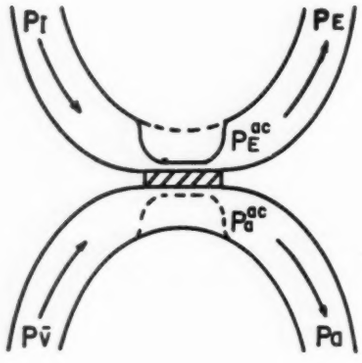

FIG. 7. Impaired distribution and diffusion.

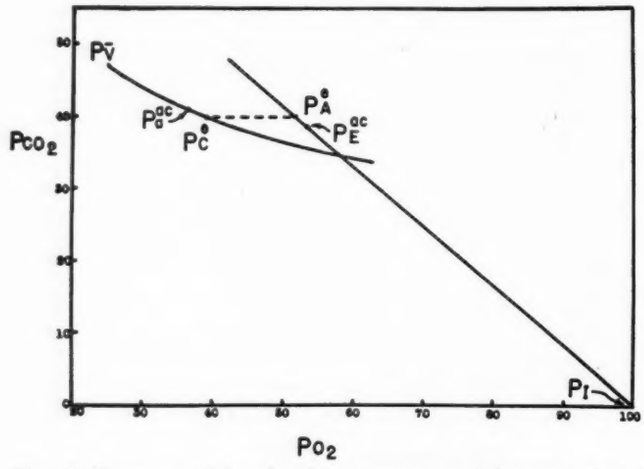

FIG. 8. Pressures of the alveolar component of the expired gas and of the alveolar component of the arterial blood.

gradient is the same, hence the same amount of oxygen diffuses in each case. The partial pressure gradient at the end of the capillary, however, is 0.1 mm. Hg at the higher level of oxygenation and 11 mm. Hg at the lower.

Returning to the comparison of the oxygen and carbon dioxide gradients at the end of the capillary, we have to deal with two principal factors which tend to balance each other. Carbon dioxide is much more diffusible, which tends to make its final gradient smaller, but the CO_2 dissociation curve is much steeper, which tends to make the final gradient larger. On theoretic grounds it appears that the slope of the oxygen dissociation curve varies enough at different levels of oxygenation to make the oxygen gradient sometimes smaller and sometimes larger than the carbon dioxide gradient at the end of the capillaries. When the P_{O_2} of inspired air is very high, a very flat portion of the oxygen dissociation curve is brought into use and the final oxygen gradient is smaller than the CO_2 gradient. When room air is breathed, the O_2 gradient is probably about the same size as the CO_2 gradient at high and low levels of oxygenation is used in estimating the diffusion characteristics of the lung in quantitative terms.

Impaired Distribution. If, in addition to impairment of diffusion, there should also be impairment in the distribution of gas and blood to the alveoli, a situation such as that represented in Figure 7 would exist. Here variation in the width of the gas and blood streams indicates distortion of the normal ratio of alveolar ventilation to blood flow in different parts of the lung.

The effects of variations in the ratio of alveolar ventilation to blood flow upon the composition of the gas and blood leaving the alveoli can readily be formulated in mathematical terms by rearranging Equations 1 and 2. Hence:

$$(5)\quad \frac{\dot{V}_A}{\dot{Q}_C} = \frac{C\bar{v}_{CO_2} - C\dot{c}_{CO_2}}{F_{A_{CO_2}} - F_{I_{CO_2}}} = \frac{C\dot{c}_{O_2} - C\bar{v}_{O_2}}{F\dot{I}^{e}_{O_2} - F_{A_{O_2}}}$$

For a given individual in a steady state the inspired gas and the mixed venous blood may be assumed to maintain a constant

composition. Accordingly, $F_{I_{CO_2}}$, $F_{I_{O_2}}$, $C\bar{v}_{CO_2}$ and $C\bar{v}_{O_2}$ remain constant, and the variations in the ratio of ventilation to blood flow ($\dot{V}_A/\dot{Q}c$) are associated with variations in the composition of the gas and blood leaving alveoli in different parts of the lung ($F_{A_{CO_2}}$, $F_{A_{O_2}}$, $C\dot{c}'_{CO_2}$ and $C\dot{c}'_{O_2}$).

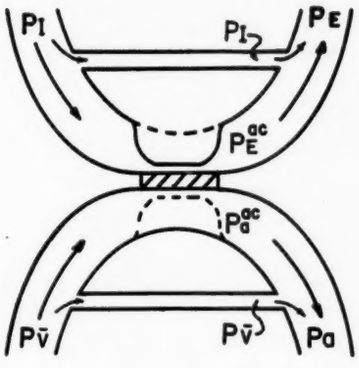

FIG. 9. True shunts (dead space admixture and venous admixture) in addition to impaired distribution and diffusion.

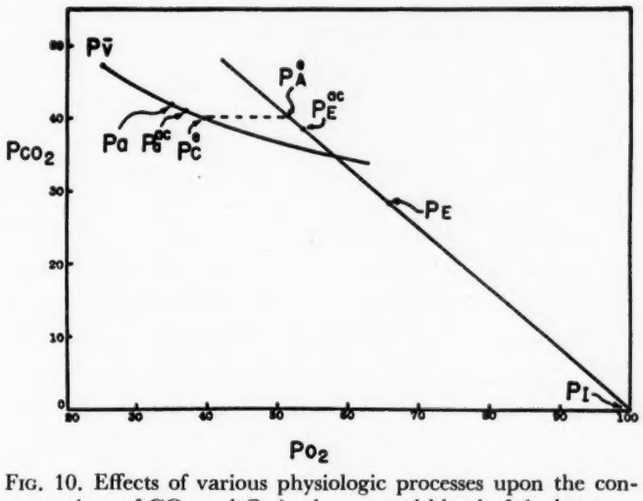

FIG. 10. Effects of various physiologic processes upon the concentrations of CO_2 and O_2 in the gas and blood of the lungs.

These equations are presented in simplified form. The complete equations are as follows:

(5a)

$$\frac{\dot{V}_A}{\dot{Q}c} = \frac{(C\bar{v}_{CO_2} - C\dot{c}'_{CO_2})(1 - F_{I_{O_2}} - F_{I_{CO_2}})}{F_{A_{CO_2}}(1 - F_{I_{O_2}}) - F_{I_{CO_2}}(1 - F_{A_{O_2}})}$$

$$= \frac{(C\dot{c}'_{O_2} - C\bar{v}_{O_2})(1 - F_{I_{O_2}} - F_{I_{CO_2}})}{F_{I_{O_2}}(1 - F_{A_{CO_2}}) - F_{A_{O_2}}(1 - F_{I_{CO_2}})}$$

No matter how great the variations in different parts of the lung, the total alveolar contributions to the expired gas and the arterial blood must necessarily have compositions which fall on the gas and blood R lines for the lung as a whole. They fall on different parts of the R lines from the "effective" points, since the latter represent values which would exist if the ratio of alveolar ventilation to blood flow were constant throughout the lung. The values for the total alveolar contributions, which we shall call the alveolar components of the expired gas (P_E^{ac}) and arterial blood ($P\bar{a}^{ac}$), are indicated in Figure 8 for a lung in which distribution is impaired.[1] Ventilation of alveoli which are poorly supplied with blood causes P_E^{ac} to be displaced from P_A^e toward P_I, and blood flow through alveoli which are poorly ventilated causes $P\bar{a}^{ac}$ to be displaced from $P\bar{c}^e$ toward $P\bar{v}$.

Admixture of Dead Space Gas to Alveolar Gas, and Venous Blood to Alveolar Capillary Blood. In Figure 9 shunts have been introduced to represent the admixture of dead space gas to alveolar gas and venous blood to the blood leaving the alveolar capillary. Since dead space gas is assumed to be identical in composition to inspired gas, this method of representing the effect of dead space gas upon the composition of the expired gas is physiologically correct. The blood shunt is an exact representation only when mixed venous blood enters the oxygenated stream unchanged. Except in the case of vascular anomalies this is not an important consideration. However, small amounts of poorly oxygenated blood from the bronchial and Thebesian veins enter the oxygenated stream leaving the alveoli. Although the composition of this blood may not be identical to that of mixed venous blood, its effect is comparable to the addi-

tion of mixed venous blood, and it is intended that this effect be included in the blood shunt shown in Figure 9.

In Figure 10 the effects of dead space admixture and venous admixture are shown on the O_2-CO_2 diagram. The mixed expired gas results from the mixture of dead space gas with the alveolar component of the expired gas; and when mixed venous blood joins the alveolar component of the arterial blood, the mixed arterial blood results. The composition of the mixed gas and blood can be represented by points on the R lines for the lung as a whole because neither of the shunted streams takes part in gas exchange and hence neither has an effect upon the ratio of CO_2 to O_2 exchange.

The effects of the gas and blood shunts upon the concentrations of respiratory gases in the mixed streams depends upon the ratio of the flow through the shunt to the total flow. The mathematical equations for the mixing effects are as follows:

$$(6)\quad \frac{\dot{V}_D}{\dot{V}_E} = \frac{F^{ac}_{E_{CO_2}} - F_{E_{CO_2}}}{F^{ac}_{E_{CO_2}} - F_{I_{CO_2}}} = \frac{F_{E_{O_2}} - F^{ac}_{E_{O_2}}}{F_{I_{O_2}} - F^{ac}_{E_{O_2}}}$$

$$(7)\quad \frac{\dot{Q}va}{\dot{Q}t} = \frac{Ca_{CO_2} - Ca^{ac}_{CO_2}}{C\bar{v}_{CO_2} - Ca^{ac}_{CO_2}} = \frac{Ca^{ac}_{O_2} - Ca_{O_2}}{Ca^{ac}_{O_2} - C\bar{v}_{O_2}}$$

where D, va and t, used as subscripts, refer to dead space, venous admixture and total blood flow, respectively.

There is a striking similarity between the effects of variations in the ratio of alveolar ventilation to blood flow and the effects of direct shunting. For the gas phase, both effects produce a linear displacement in the same direction along the gas R line. For blood both effects produce a linear displacement in the same direction along the blood R line when the R line is plotted in terms of the concentrations of respiratory gases in blood. When, as in Figure 10, the blood R line is transposed into terms of partial pressure, the linear relationship is concealed. The fact of basic importance is that the net effect of variations in the distribution of gas and blood to the alveoli is identical with that which would result, in the absence of impaired distribution, if shunts of dead space gas and mixed venous blood existed.

Since the effects of impaired distribution can be described in terms of an equivalent effect due to dead space admixture or venous admixture, it is convenient to quantitate the distribution effect in this way. The distribution effect upon the gas phase and the dead space admixture effect may be combined, and the distribution effect upon the blood may be combined with the venous admixture effect. In each case the combined effect is expressed as a proportion of total flow shunted.[1]

The equations for the dead space and venous admixture effects, in the expanded sense, are the following:

$$(8)\quad \frac{\dot{V}_D}{\dot{V}_E} = \frac{F^{e}_{A_{CO_2}} - F_{E_{CO_2}}}{F^{e}_{A_{CO_2}} - F_{I_{CO_2}}} = \frac{F_{E_{O_2}} - F^{e}_{A_{O_2}}}{F_{I_{O_2}} - F^{e}_{A_{O_2}}}$$

$$(9)\quad \frac{\dot{Q}va}{\dot{Q}t} = \frac{Ca_{CO_2} - Cc^{e}_{CO_2}}{C\bar{v}_{CO_2} - Cc^{e}_{CO_2}} = \frac{Cc^{e}_{O_2} - Ca_{O_2}}{Cc^{e}_{O_2} - C\bar{v}_{O_2}}$$

Total Ventilation. The effect of total ventilation upon the concentrations of carbon dioxide and oxygen in the lungs can be visualized in Figure 10. The larger the ventilation, the smaller the gradient between inspired and expired gas becomes, assuming that over-all metabolism remains constant. Since the inspired gas composition is fixed, the composition of the expired gas approaches that of the inspired gas. In producing this effect an increase in ventilation alters not only the expired gas but all the other values shown in Figure 10. They all move downward and to the right indicating an increase in O_2 concentration and a decrease in CO_2 concentration. Change in the expired gas reflects a change in the alveolar gas, which in turn is associated with a change in the blood leaving the alveolar capillaries and hence in the arterial blood and in the venous blood.

The effect of total ventilation ($\dot{V}_E$) upon the expired gas is readily derived from the following equations:

$$(10) \qquad \dot{V}_{CO_2} = \dot{V}_E(F_{E_{CO_2}} - F_{I_{CO_2}})$$

$$(11) \qquad \dot{V}_{O_2} = \dot{V}_E(F^c_{I_{O_2}} - F_{E_{O_2}})$$

These are the basic equations by which CO_2 output and O_2 intake are ordinarily calculated. If $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ remain constant, the values within the parentheses vary inversely with ventilation, and the values within the parentheses, when transposed into terms of partial pressure, represent the inspired-expired gradients shown in Figure 10.

Total Blood Flow. A change in total blood flow alters the arteriovenous gradient. If over-all metabolism remains constant, an increase in blood flow causes the composition of the mixed venous blood to approach that of the arterial blood. A change in blood flow may also alter blood-gas distribution if, for example, the increased blood flow passes through poorly ventilated alveoli. Diffusion relationships may also be altered since an increase in blood flow may lead to an increase in the number of capillaries perfused and hence to an increase in the diffusing surface of the lungs. Theoretically, these effects upon distribution and diffusion may lead to changes in the composition of alveolar gas, alveolar capillary blood and arterial blood.

The relationship between rate of blood flow and arteriovenous gradient can be derived from the following equations:

$$(12) \qquad \dot{V}_{CO_2} = \dot{Q}t(C\bar{v}_{CO_2} - Ca_{CO_2})$$

$$(13) \qquad \dot{V}_{O_2} = \dot{Q}t(Ca_{O_2} - C\bar{v}_{O_2})$$

These are the relationships of Fick which may be used in determining cardiac output. When $\dot{V}_{CO_2}$ and $\dot{V}_{O_2}$ remain constant and when the values within the parentheses are transposed into terms of partial pressure, the inverse relationship between blood flow and arteriovenous partial pressure gradient becomes apparent.

This concludes the description of the effects of diffusion, distribution, ventilation and blood flow upon the concentrations of carbon dioxide and oxygen in the gas and blood of the lungs.

COMMENT

The values which are used to define representative concentrations of CO_2 and O_2 in the alveolar gas and alveolar capillary blood are of critical importance in the quantitative estimation of diffusion and distribution characteristics in patients with pulmonary disease. For example, the calculation of a representative *mean* gradient between alveolar gas and capillary blood from which diffusion characteristics can be quantitated requires knowledge of the gradient at the end of the capillary. This gradient may vary in different parts of the lungs because of variations in both the alveolar gas and the blood leaving the alveolar capillary. The latter variations, in turn, may be due in part to local variations in diffusing characteristics and in part to local variations in the ratio of ventilation to blood flow. These factors can be singled out only by the use of calculated values, such as the "effective" alveolar gas and the "effective" capillary blood, which reflect the over-all diffusion characteristics of the lung as a whole but which are unaffected by imperfect distribution. Such calculated values are essential to the analysis of distribution as well as to the analysis of diffusion, for the degree of impairment of distribution must be related to the conditions which would exist if distribution were perfect. On theoretic grounds it would therefore appear that the ability to determine the "effective" alveolar gas and the "effective" capillary blood is a prerequisite to the quantitative analysis of diffusion and distribution in patients with pulmonary disease.[3]

Methods for the quantitative estimation of diffusion and distribution characteristics have been developed to a point where they yield a useful degree of accuracy. They are based upon the simultaneous sampling and analysis of inspired gas, expired gas, arterial blood and mixed venous blood. CO_2 output, O_2 intake, total ventilation and total blood flow are then readily determined. The remaining problem is to determine "effec-

tive" alveolar gas and "effective" capillary blood. These values cannot be obtained by direct alveolar sampling since they represent the hypothetic values which would exist if the distribution of gas and blood to alveoli in different parts of the lung were perfect. An indirect approach is therefore inescapable. This approach is based upon the fact that the partial pressure gradients which are related to the distribution and diffusion characteristics vary at different levels of oxygenation because of the changing slope of the oxygen dissociation curve, whereas the underlying distribution and diffusion characteristics of the lung itself may reasonably be assumed to remain constant if the patient's metabolic state remains unchanged and severe degrees of hypoxia are not imposed. The distribution characteristics of the lung, which are assumed to remain constant under the conditions of the experiment, are the ratio of dead space ventilation to total ventilation ($\dot{V}_D/\dot{V}_E$) and the ratio of venous admixture to total blood flow ($\dot{Q}va/\dot{Q}t$); the diffusion characteristic, which is assumed to remain constant under the conditions of the experiment, is the mean partial pressure gradient between alveolar gas and alveolar capillary blood ($P^{e}_{A_{O_2}} - \bar{P}c_{O_2}$). If these relationships do in fact remain essentially constant when studies are performed at two properly chosen levels of oxygenation (and there is evidence which suggests that they do) and if the direct analyses mentioned above are made at both levels, the "effective" alveolar gas and capillary blood can be determined at each level, and the diffusion and distribution characteristics can be determined quantitatively.[5]

The quantitative evaluation of distribution and diffusion characteristics involves a further assumption which is rarely of practical importance but is of considerable theoretic interest. This assumption is that the CO_2 diffusion gradient at the end of the alveolar capillary is never of significant magnitude, i.e., that it never exceeds 1 mm. Hg. This assumption is untrue if such dense fibrous tissue is interposed between the alveolar capillary and the alveolar gas that virtually no gas exchange whatever can take place. However, it can be argued that the phenomenon of blood passing through such a capillary should be classified as impaired distribution of blood flow rather than impaired diffusion since to all intents and purposes venous blood is shunted into the oxygenated stream without exposure to the alveolar gas. One is forced to the conclusion that the very concept of impaired diffusion is indistinguishable from the concept of impaired distribution in extreme cases. For practical purposes an arbitrary division between the two must be made. We have elected to consider processes producing an appreciable CO_2 gradient at the end of the capillary to be the result of impaired distribution, since virtually no oxygen diffuses across such capillaries unless the *mean* oxygen gradient is very large indeed. For the study of normal subjects and the vast majority of patients with pulmonary disease, the arbitrary dividing line between distribution and diffusion introduces no theoretic or practical difficulties.[1]

The diffusing capacity of the lung for oxygen, which is the amount of oxygen diffusing across the alveolar membrane per mm. Hg oxygen pressure gradient, is calculated by dividing the oxygen intake, in ml. per minute, by the *mean* pressure gradient between alveolar gas and alveolar capillary blood. The diffusing capacity, like the *mean* gradient, remains constant when two moderately different concentrations of oxygen are breathed, provided the subject remains in the same steady state. Both diffusing capacity and *mean* gradient are dependent upon the diffusibility of the gas per unit area and upon the total area across which gas diffuses. The diffusibility of gas across a unit area of alveolar membrane can be altered by disease processes. A thickening of the layers across which the gas must diffuse can usually be seen in a microscopic section in such cases. The total functioning area of alveolar membrane is the total area of the alveolar capillary walls across which

gas diffuses. The number of perfused capillaries passing through ventilated alveoli thus determines the functioning area of alveolar membrane. This area is by no means constant and probably increases several-fold as a result of increased ventilation and increased cardiac output during strenuous exercise. Increase in the area of the diffusing surface is probably the principal fact accounting for the four-fold increase in diffusing capacity which has been found during strenuous exercise[4] and for the low diffusing capacity which is found when the cardiac output is low.[6] The concept of an expansible vascular bed helps in the understanding of many pulmonary phenomena, including the repeated observation that in normal lungs the pulmonary arterial pressure does not increase until the blood flow has increased to approximately three times the normal resting level.[7–9] Because the diffusing capacity is capable of normal physiologic change as well as pathologic change, it is a difficult value to interpret in the resting state unless it is grossly abnormal. The maximal diffusing capacity during exercise would be more significant and more easily interpreted, but this value is as yet difficult to determine.

The concept which implies that distribution is the ratio of alveolar ventilation to alveolar blood flow is different from the more familiar concept in which distribution is associated with intrapulmonary mixing in the gas phase alone. We have emphasized the former concept because it provides an opportunity to discuss the theoretic aspects of various alveolar processes which are directly concerned with gas exchange.

From the practical point of view the determinations which have been outlined merely amplify interpretations which have previously been made on the basis of more familiar technics. Much of the basic understanding of the altered physiology in pulmonary disease has come from such determinations as the following: lung volumes and maximal ventilatory capacity,[10–14] the ratio of residual volume to total capacity,[10,11,15,16] the rate of nitrogen removal and other inert gas mixing tests,[11,17–20] the rate of oxygen removal per L. ventilation or its reciprocal, the ventilatory equivalent,[21,22] the respiratory dead space and its relation to tidal volume,[11,20,23,24] the breathing reserve during rest and exercise and its relation to maximal ventilatory capacity,[21] bronchospirometric determinations of ventilation and gas exchange in each lung separately[25–28] and more recently the recording of ventilatory flow rate and alveolar pressure.[29–33] These determinations and many others are primarily related to ventilation and the distribution of ventilation to the alveoli although some of the tests throw indirect light upon the distribution of blood blow. The alveolar gas can be sampled directly by various technics.[34–36] The oxygen saturation of the arterial blood at rest and after exercise,[14] and more recently the saturation time and saturation tension tests,[37,38] are used to explore pulmonary function with reference to the blood leaving the lungs. The diffusing capacity can be determined by the carbon monoxide method.[39] Finally, the development of technics for cardiac catheterization makes available direct information regarding the composition of the blood entering the lungs.[40]

It is appropriate to apply direct information which can now be obtained regarding the composition of gas and blood entering and leaving the lungs to the analysis of the intermediate processes taking place within the alveoli in different parts of the lungs. The method of presentation which has been adopted here has been aimed at elucidating this possibility and at the same time clarifying the understanding of the physiologic processes involved. These processes constitute basic factors in gas exchange.

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Clinico-pathologic Conference

Myocardial Infarction Terminating Fatally

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, E. K. (No. 186678), a white married office worker, fifty-two years of age, entered the Barnes Hospital July 6, 1950, complaining of pain in the chest. The patient was too ill to give his own history and the information available was secured from his wife. The family history was irrelevant. In the past history it was noted that the patient had had "spastic colitis" for several years. A vague history of penicillin hypersensitivity was obtained. One year before entry he had dizziness which disappeared after irrigation of the nasal sinuses. Three months prior to entry a complete gastrointestinal x-ray series was reported as negative. The patient had been a heavy smoker for years and had drunk large amounts of beer.

Three weeks before entry the patient suffered the first of several attacks of severe substernal pain which radiated down his left arm. Each episode occurred after exertion. He consulted his physician who advised him to cut down on smoking; the patient complied and reported that the decrease in tobacco consumption definitely ameliorated his symptoms. Three electrocardiograms taken by his physician were normal.

At 4 A.M. on the day of admission the patient was awakened from sleep by a very severe pain in the chest which radiated to the left shoulder. He was given morphine, which brought partial relief, and was sent to the hospital.

At the time of entry physical examination revealed the temperature to be 36.4°C., pulse 104, respiration 24 and blood pressure 110/80. The patient was an obese man who appeared anxious and was very dyspneic. He complained of severe substernal pain. He was perspiring freely and the skin and nail beds were slightly cyanotic. The pupils were pinpoint in size and the fundi were not seen. The upper respiratory tract examination was deferred. The neck veins were slightly distended with the patient sitting at a 45 degree angle. Examination of the lungs revealed diffuse coarse rales bilaterally but no localizing signs were present. The heart size was percussed at the upper limits of normal with the left border dullness being in the fifth interspace. The rhythm was regular, the rate rapid. The sounds were of poor quality and were obscured by numerous rales; no murmurs were heard. The abdomen was obese but no masses or organs were palpable and there were no signs of peritoneal irritation. Slight pitting edema was noted.

The laboratory data were as follows: Blood count: red cells 5,930,000; hemoglobin, 18 gm.; white cells, 29,100; differential count: juvenile forms, 2 per cent; stab forms, 5 per cent; segmented forms, 73 per cent; lymphocytes, 20 per cent. The patient was incontinent and a urine specimen was not obtained. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 21 mg. per cent; sugar, 139 mg. per cent; prothrombin time, 53.5 per cent of normal. Sedimentation rate: 11 mm./hr. Electrocardiogram: evidence of extensive anterior myocardial infarction.

The patient was given additional morphine and atropine and placed in an oxygen tent. Two hours after entry his pain decreased somewhat. At that time he was given demerol, intravenous aminophyllin and dicumarol. During the first hospital day

the rales decreased, but the patient was extremely nauseated and vomited what liquids he was given. During the course of the first night his blood pressure ranged between 85/65 and 95/85, and the pulse was weak and thready. The patient continued to have some chest pain during the entire first hospital day although cyanosis disappeared. During the second day the chest pain was still present and the cough, present on admission, increased; the patient produced a small amount of bloody sputum. The heart sounds remained poor in quality. The pulse rate varied from 105 to 120 and the blood pressure was 85/65 mm. Only slight dyspnea was noted. The pulmonary rales persisted and were more prominent on the left. No edema was present.

During the course of the second hospital day the patient became somewhat disoriented but remained alert. During the afternoon of the second day his temperature rose to 39°C. and chloromycetin therapy was begun. During his second night in the hospital the chest pain localized to the left lower chest, became more severe and was aggravated on deep breathing. Rales persisted at both lung bases but no other localizing signs were noted. During the night the pulse and blood pressure were scarcely obtainable. The patient was given demerol for pain. On the morning of the third day rales had greatly increased over the right lower lobe. An electrocardiogram was unchanged from that recorded on admission. Following dicumarol therapy the prothrombin time fell to 27 per cent of normal. During the third evening the patient became extremely dyspneic and cyanosis appeared. At that time the temperature was 38.5°C., the pulse 150, respiration 36 and blood pressure 80/60 mm. The patient was quite agitated.

Little change was apparent during the fourth hospital day except that the patient's temperature rose to 41.2°C. During the course of the day Cheyne-Stokes respiration appeared. Rales persisted in both lungs. Following negative scratch and intradermal tests for penicillin sensitivity the drug was begun in doses of 100,000 units every three hours. During his entire hospital stay the patient had continued to vomit anything he was given by mouth. The pulse rate varied between 130 and 180 and the heart sounds continued to be barely audible. Peripheral pulses were felt only in the feet. The patient continued to be incontinent during his hospital stay and produced only slight amounts of urine. On July 11, 1950, shortly after having been seen by a house officer who noted no new findings, the patient expired.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: It seems certain that this patient suffered from coronary artery disease; and since this form of heart disease is an extremely common and important one, it seems fitting to discuss the problem. A number of factors in this particular case merit discussion. The patient was fifty-two years old, obese, a male and a heavy smoker. Apparently until three weeks before admission there was no indication that he had any heart disease whatsoever. He then developed anginal pain on exertion which was partially relieved presumably after he reduced his smoking. It is interesting to note that three electrocardiograms in this period were normal. Dr. Massie, would you comment on the occurrence of normal electrocardiograms in such a situation.

DR. EDWARD MASSIE: It is not uncommon to see patients with typical angina pectoris whose electrocardiograms are normal. It may be stated that abnormalities are more often picked up when, in addition to the standard leads, the various unipolar leads are also employed. But it is perfectly possible, and unfortunately not unusual, even with complete electrocardiographic study, for such patients as this one to show no abnormality. It is apparent therefore that a careful history is most important when one suspects the possibility of angina in a patient whose electrocardiographic tracings are normal. A procedure which may be

helpful in this regard is the "two-step test" which Master has described. If one uses the Master test in patients in whom the diagnosis of angina is suspected but whose electrocardiograms at rest are normal, one may frequently demonstrate abnormalities.

DR. CARL V. MOORE: Dr. Alexander, can we ask Dr. Massie whether it would have been valuable with the patient under discussion to obtain electrocardiographic tracings after he had smoked several cigarettes?

DR. MASSIE: Although it is quite clear that patients with coronary artery disease are well advised to decrease or discontinue smoking, smoking is unfortunately not a good test for coronary insufficiency. We studied many patients who were heavy smokers and attempted to demonstrate significant electrocardiographic changes during smoking. None could be found.

DR. ALEXANDER: Would you define angina pectoris, Dr. Massie.

DR. MASSIE: By the term angina pectoris we refer to chest pain which usually accompanies exertion, is of short duration and may or may not radiate to either arm or shoulder. It is relieved promptly by rest, nitroglycerin or some other vasodilator. Had this patient had electrocardiograms made during an attack of angina, objective evidence, such as inversion of T waves in the precordial leads, probably could have been demonstrated. Such changes are indicative of ischemia of the myocardium but do not indicate in themselves irreversible damage.

DR. ALEXANDER: Does the diagnosis of angina pectoris imply pathologic changes in the coronary arteries?

DR. MASSIE: That would usually be true, although there are certain situations in which patients with normal coronary arteries may experience angina. For example, in the presence of severe anemia angina may occur in patients with normal coronary circulation.

DR. ALEXANDER: I should now like to ask Dr. Smith to comment on the effect of smoking in patients with coronary disease.

DR. JOHN R. SMITH: The available evidence suggests that in an individual with normal coronary arteries the consumption of tobacco is not harmful to the heart, although it is well established that extensive use of tobacco results in at least a minor degree of generalized vasoconstriction. Presumably the vasoconstrictor action is due to the nicotine. In the presence of vascular disease, particularly in Buerger's disease, the vasoconstricting effect of tobacco may become important in that constriction of arteries may result in serious functional impairment in circulation. In such patients the use of tobacco is unwise and should be discontinued.

DR. ALEXANDER: Dr. Massie, when this patient was admitted to the hospital the electrocardiogram showed evidence of an anterior myocardial infarction. Would you discuss the changes noted at that time.

DR. MASSIE: I believe a better description of the tracings obtained would be "a massive infarction." In almost every lead there was evidence of profound change. In standard lead I the S-T segment was elevated, and in standard leads II and III marked depression of the S-T segments was present; thus even with the three standard leads alone there was striking evidence that this patient had a very extensive myocardial infarction. In aV_L, the left arm extremity lead, the S-T segment was markedly elevated whereas it was strikingly depressed in aV_F. In the precordial leads elevation of the S-T segments was noted from V_1 through V_6, indicating myocardial injury. Death of muscle was indicated by the Q waves in leads I, aV_L and in the V leads. The extensiveness of the V lead abnormalities indicated that the infarction was massive and anterior in location.

DR. ALEXANDER: Can we assume therefore that the diagnosis of myocardial infarction is certain?

DR. MASSIE: The only other possible cause of such electrocardiographic abnormalities would be an extremely large metastasis in the entire anterior myocardial

wall. In this case there is nothing to suggest that possibility.

DR. ALEXANDER: Dr. Schroeder, this patient had signs of cardiac decompensation as manifested by dyspnea, cyanosis and edema. Do you believe digitalis should be used in cardiac failure complicating myocardial infarction?

DR. HENRY A. SCHROEDER: That question is an extremely difficult one which has been debated for years. In the presence of myocardial infarction digitalis must certainly be used with extreme caution since the irritable myocardium may become the site of ventricular tachycardia or ventricular fibrillation. In general it is thought by many that digitalis should be used only under the most extreme circumstances, that is, when cardiac failure becomes the major threat. From the protocol I would assume that this man's failure was not terribly severe; it was chiefly left-sided as evidenced by persistent pulmonary congestion. Actually the pitting edema which was present on admission subsequently cleared. In my opinion situations like this are usually best handled by omitting digitalis and by rigidly restricting salt.

DR. ALEXANDER: Does anyone dissent?

DR. SMITH: I should like to emphasize Dr. Massie's remarks in regard to the extreme degree of myocardial damage exhibited by this patient and would agree on that basis that it would have been very dangerous to use digitalis.

DR. SCHROEDER: In regard to salt restriction, Dr. Alexander, the use of mercurial diuretics is indicated in cases such as this one. In choosing a mercurial one should avoid those preparations which are combined with a xanthine.

DR. MOORE: Would Dr. Smith comment on the use of oxygen in myocardial infarction.

DR. SMITH: I believe oxygen should be given patients with myocardial infarction. It acts as a vasodilator and as a result often relieves pain, even when large doses of morphine have not irradicated it entirely. Occasionally such patients are also greatly benefited by papaverine in doses of 60 mg.

DR. SCHROEDER: In regard to oxygen therapy, Dr. Alexander, I should like to suggest the use of partial pressure oxygen if the patient can tolerate it. Certainly in a patient like this man, with pulmonary congestion, it is clear that pressure breathing will tend to be helpful.

DR. ROBERT J. GLASER: What about the use of positive pressure oxygen in a patient who is in or almost in shock, Dr. Schroeder? Isn't positive pressure oxygen contraindicated in such a patient?

DR. SCHROEDER: Your point is well taken. Positive pressure oxygen does reduce the effective circulating blood volume. Because it tends to prevent pulmonary filling, it also lessens right heart input. I would agree that in peripheral circulatory collapse or in severe hemorrhage it should not be employed but in a situation like this one a choice of the lesser of two evils must be made and it might have been helpful.

DR. JOSEPH C. EDWARDS: Positive pressure oxygen is helpful over short periods but used over longer periods it is apt to be identified with secondary irritation in the respiratory tract.

DR. SCHROEDER: It is true that oxygen poisoning can occur in normal persons given 100 per cent oxygen, particularly positive pressure oxygen, over a long period of time. However, under circumstances such as were extant in this case, when it is used for only a few days, that complication is not dangerous.

DR. GLASER: Dr. Alexander, could we ask Dr. Moore to comment on the amount of effective oxygen a patient gets when in a tent. One of the problems in using a mask, the most efficient method, is that patients often tolerate it poorly.

DR. MOORE: If a tent is correctly used one may get oxygen concentrations up to about 40 per cent. However, it is fair to point out that an oxygen tent is almost never used correctly and that frequently the oxygen content is usually only 25 or 30 per cent and is therefore of little value.

In regard to the toxicity of positive pressure oxygen I believe we may be overcautious in that regard. Certainly if a patient got only 100 per cent oxygen, toxicity would be seen. On the other hand, even with a good mask, the oxygen concentration is not maintained at 100 per cent and thus the danger of pulmonary irritation is minimal.

DR. LLEWELLYN SALE, JR.: I should like to ask Dr. Smith about the toxic effects of intravenous papaverine. It has been reported that arrythymias, standstill and death have occurred after intravenous administration of the drug.

DR. SMITH: As I recall, those complications occurred after high doses of papaverine. Probably the dose given at one time should be limited to 60 mg.

DR. ALEXANDER: What about the use of aminophyllin?

DR. SMITH: Aminophyllin exerts its beneficial effects upon the heart largely through stimulation of contraction; thus it has a transient digitalis-like effect on the myocardium producing more powerful systole. Under the circumstances such as were present here, it may be dangerous.

DR. ALEXANDER: Are there any further comments?

DR. DEAN F. DAVIES: It is evident that this man had congestive heart failure, and also that he was on the brink of shock. The exact status of the patient's hemodynamics should be clarified so that treatment may be properly directed. In this regard, it is important to note that in approximately 75 per cent of the patients admitted to the Barnes Hospital with myocardial infarction hypertension has been a concomitant finding. We have no evidence that this patient did not have hypertension; thus very possibly the admission blood pressure of 110/80 may have indicated that he was actually in shock. Subsequently, when his pressure fell to 85/65 and remained at that level for the rest of his course, he actually may have been in severe shock. Would Dr. Smith comment on this possibility?

DR. ALEXANDER: It is of interest that his red count was 5,800,000 with 18 gm. of hemoglobin. Dr. Smith, do you believe that the patient was in shock?

DR. SMITH: Yes, I believe he was. Many patients with myocardial infarction exhibit varying degrees of shock. In an experimental animal, when a critical amount of damage to the myocardium is inflicted, the blood pressure goes down just as it does in humans who suffer myocardial infarction. In the experimental animal, blood transfusions often will not result in a return of the blood pressure to normal.

DR. ALEXANDER: This patient's white count was 29,000 when he came in. Is that unusual for myocardial infarction, Dr. Moore?

DR. MOORE: No, I do not believe so. There are two factors which may have been operating. First, necrosis of muscle may give rise to leukocytosis and, second, the acute stress may have induced increased epinephrine production and resulted in the leukocytosis and high fasting blood sugar of 139 mg. per cent.

DR. ALEXANDER: What about the occurrence of high fever? Is that seen in uncomplicated myocardial infarction?

DR. MOORE: It can happen but it is conceivable that the patient had bronchopneumonia as well.

DR. ALEXANDER: Do you believe those findings were unusual, Dr. Massie?

DR. MASSIE: No, I do not think so. As Dr. Moore suggests they could have been explained on the basis of infarction alone or with associated pulmonary infection. The white count and the temperature were both higher than usual but, on the other hand, this man had a more severe infarction than many that are seen.

DR. ALEXANDER: This patient vomited everything he was given by mouth throughout his hospital course. What is your explanation for the repeated vomiting, Dr. Edwards?

DR. EDWARDS: Vomiting may be seen in patients with severe pain and in those who are on the brink of shock. In addition, the patient received rather large amounts of narcotics which also often produce emesis.

Finally, in congestive failure vomiting is sometimes seen.

DR. ALEXANDER: Dr. Massie, do you believe that morphine and demerol were responsible for the vomiting?

DR. MASSIE: As Dr. Edwards indicates, patients who have a massive infarction may vomit even before they receive morphine, but certainly morphine may cause vomiting.

DR. ALEXANDER: Do you believe cardiac failure *per se* could explain it?

DR. MASSIE: No, I do not think so. Everything that happened to this patient was very severe and I would therefore think that the vomiting may merely represent another aspect of his general reaction.

DR. ALEXANDER: Up to this point everything about the patient's course seems compatible with a very severe myocardial infarction. In regard to the terminal episode, however, it is interesting to note that the patient was seen by a house officer fifteen minutes before death. At that time although he was still in the critical state which characterized his course, his condition did not appear to be terminal. When the house officer returned fifteen minutes later, the patient was dead. What suggestions can be offered in regard to the cause of death?

DR. SCHROEDER: Certainly ventricular fibrillation or cardiac standstill are possibilities.

DR. ALEXANDER: Both are very common. Are there any other suggestions?

DR. MASSIE: Ventricular rupture might well have occurred in a patient with such a massive infarct.

STUDENT: Pulmonary infarct.

DR. ALEXANDER: That certainly should be considered.

DR. KEITH S. WILSON: Death could have resulted from shock alone.

DR. SEDGWICK MEAD: Dr. Alexander, on what day after myocardial infarction is rupture most likely to occur?

DR. ALEXANDER: Will you answer that question, Dr. Massie?

DR. MASSIE: It may occur any time between the third and twenty-first days.

DR. ALEXANDER: Are there any other questions?

DR. CARL G. HARFORD: Will you comment on the use of scratch and intradermal tests to eliminate the possibility of penicillin hypersensitivity.

DR. ALEXANDER: I do not believe that negative tests would eliminate it.

DR. CHARLES A. ROSS: Dr. Schroeder said that digitalis should be used as a last resort. I would like to ask whether, in retrospect, digitalis should not have been used here? It seems to me that he had a serious degree of cardiac decompensation before he died.

DR. ALEXANDER: Would you comment, Dr. Schroeder?

DR. SCHROEDER: It is my personal belief that it is more benign to "pull the fluid out" rather than to "push it out." The fluid may be pushed out if one improves the myocardium, or it can be pulled out if one stimulates the kidneys to excrete it. Certain of the mercurial diuretics, as I have indicated, will produce fluid excretion without increasing the work of the heart.

DR. ALEXANDER: In summary then, it seems clear that this patient had a severe myocardial infarction with cardiac decompensation, possible bronchopneumonia and, as a terminal episode, ventricular fibrillation, ventricular standstill, rupture of the ventricular wall or pulmonary infarction.

Clinical Diagnoses: Massive anterior myocardial infarction; cardiac failure; ? bronchopneumonia; ? rupture of the myocardium; ? pulmonary infarction.

PATHOLOGIC DISCUSSION

DR. RICHARD L. SWARM: On opening the peritoneal cavity serofibrinous peritonitis, with 300 cc. of bile-stained fluid, was found localized about the first portion of the duodenum. A perforated ulcer, 1.5 cm. in diameter, was present in the anterior wall of the first portion of the duodenum. The perforation was perfectly round; its edges were bile-stained and not indurated. Many small ulcerations covered by a dull fibrinous exudate involved the surrounding

mucosa. The rest of the intestine was normal except for many small diverticuli in the descending colon.

The heart was moderately enlarged (580 gm.) and dilated. Over the anterior surface there was marked fibrinosanguineous pericarditis. The descending branch of the left coronary artery was occluded 2 cm. from its orifice by a red thrombus. The walls of all the coronary arteries were sclerotic to an advanced degree, but there were no other occlusions. A yellow-red recent infarct involved the myocardium of the anterior portions of the septum and the left ventricle from the apex to the mitral ring, including the anterior papillary muscle. To gross inspection the infarct extended through the entire thickness of the left ventricle and in its center caused a distinct thinning of the ventricular wall. There was a mural thrombus adherent to the endocardial surface over the area of infarction. In the other vessels of the body the arteriosclerosis was advanced only in the abdominal aorta.

The lungs were heavy and edematous. There were no infarcts or thrombi in the pulmonary arteries. Each pleural cavity contained about 100 cc. of clear fluid, but the surfaces showed no fibrin. In the liver the lobular architecture was slightly accentuated with small yellow foci in the central portions. The spleen was slightly enlarged and congested. The kidneys were remarkable only for their finely granular surfaces.

Dr. Gustave J. Dammin: The complete occlusion of the proximal portion of the descending branch of the left coronary artery by a recent thrombus resulted in an extensive degree of damage to the myocardium that was impressive on gross inspection alone. In many parts of the wall of the left ventricle the destruction of muscle was so complete that the area had the appearance of extensive hemorrhage. The reduction of the thickness of the myocardium to just a few millimeters and the extensive fibrinous exudate provoked by extension of the necrosis to the epicardium suggest there was actually an impending rupture of the heart. Such a state on the sixth day following onset of the occlusion, as judged by the clinical history, would be quite compatible with the experiences in our autopsy series. In most of our cases rupture occurred on the sixth or seventh day, seldom later and rarely earlier.

The coronary arteries in this heart were interesting in that they had the distribution of what Schlesinger* has designated as group I; that is, the right coronary artery supplied the wall of the right ventricle, posterior portion of the interventricular septum and a portion of the left ventricular wall, in contrast to the situation in what he named group II in which the right coronary artery supplies the right ventricle and the posterior septum or group III in which the circumflex branch of the left coronary artery supplies the posterior septum. In his studies, hearts with group II circulatory patterns often contained multiple infarcts of varying ages which suggests that survival of the first myocardial infarction is the rule in patients of this group. In group III, on the other hand, none of forty-one patients recovered from the initial infarct. Hearts with the group I coronary distribution, as in this case, seem to occupy an intermediate position with many containing evidence of multiple infarcts. The ability to survive myocardial infarction is related especially to the development of anastomoses between the two coronary arteries which, although favored or made more difficult by the original anatomic pattern, is brought about by previous gradual occlusions of branches of those arteries by sclerotic plaques. This patient, unfortunately, does not seem to have developed such gradual previous occlusions as the arteries, although rigid and sclerotic, were patent. There also was no focal fibrosis in the myocardium to indicate any previous episode which might have

* Schlesinger, M. J. Relation of anatomic pattern to pathologic conditions of the coronary arteries. *Arch. Path.* 30: 403, 1940; and Blumgart, H. L., Schlesinger, M. J. and Davis, D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction to the pathologic findings. *Am. Heart J.*, 19: 1, 1940.

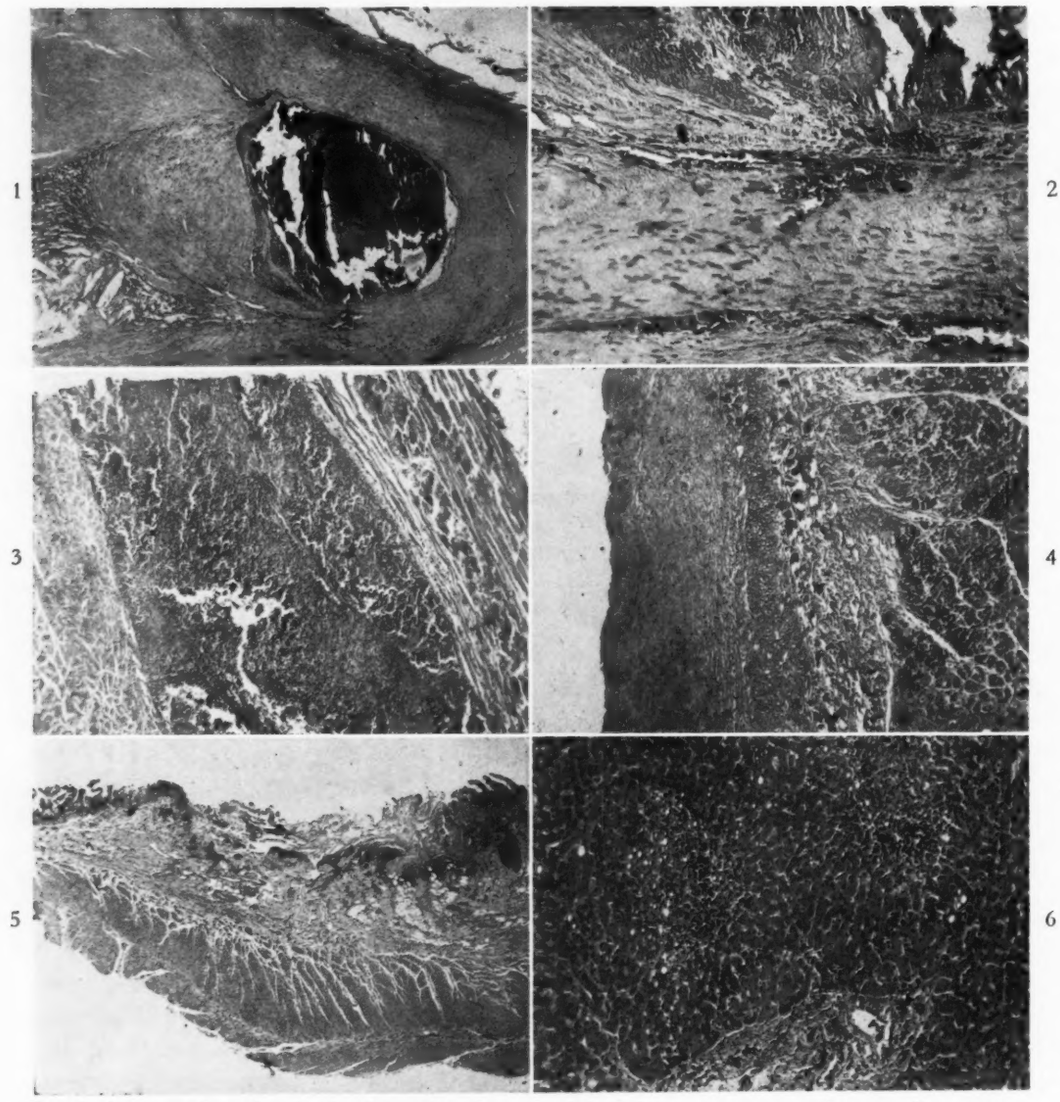

FIG. 1. A recent thrombus in the descending branch of the left coronary artery. It was adjacent to an arteriosclerotic plaque and there was hemorrhage into clefts at the edge of the plaque.
FIG. 2. Detail of the edge of the coronary thrombus and hemorrhage into the clefts in the adjacent plaque. There were small vessels in the media about the plaque which were possible sources of hemorrhage and subsequent initiation of the thrombus.
FIG. 3. A broad zone of hemorrhage and total destruction of the myocardium in the center of necrotic muscle in the major infarct.
FIG. 4. Endocardial surface of the left atrium; the immediately underlying muscle was totally destroyed and the outer layers were necrotic.
FIG. 5. The edge of the acute perforating ulcer of the duodenum. The fibrin, edema and cellular infiltration indicated this was more than a terminal event.
FIG. 6. Focal necrosis in the centers of the hepatic lobules, a lesion that not uncommonly accompanies extensive myocardial infarction.

stimulated anastomoses between the two circulations.

Figure 1 is of a section through the thrombus in the descending branch of the left coronary artery. It is apparent that the thrombus was well formed and associated with an arteriosclerotic plaque. In the lower portion of the figure it can be seen that there was hemorrhage extending between layers of the plaque. Figure 2 illustrates this situation with higher magnification and also shows some small vascular channels in the arterial wall. Such channels are commonly present about arteriosclerotic plaques, and

hemorrhage from them into the plaque with subsequent occlusion of the artery is one of the recognized mechanisms by which thrombosis is initiated. It would be difficult, however, to be certain that such a sequence occurred in this case as the cross section of the lumen was so little encroached upon by the elevated portion of the plaque.

A broad zone of actual hemorrhage in the infarcted myocardium is illustrated in Figure 3 in which necrotic muscle borders the hemorrhage on the left and disrupted although not totally dead muscle on the right. Figure 4 is from the endocardial surface of the left atrium. There was a zone of destruction of muscle immediately beneath the endocardium; the remainder of the fibers were actually necrotic although that is not too clear in this illustration. Infarction of the atrium is probably more common than is generally recognized. Cushing and associates* reported an incidence of 17 per cent in cases of ventricular infarction, but it almost always occurs in the right atrium rather than the left.

A section of the duodenum near the edge of the perforating ulcer is illustrated in Figure 5. There was loss of the mucosa, fibrin over the base of the ulcer, and considerable edema and cellular infiltration in the submucosa. The other unperforated ulcers had the same characteristics. Such histologic changes indicate that these ulcers, although acute, were of at least several days' duration. They are reminiscent of the acute perforating ulcers known as Curling's ulcers† that follow extensive burns of the skin; the comparison is perhaps more valid than appears at first glance as in both situations there has been an extensive destruction of tissue and shock or at least hypotension. No relationship between the occurrence of myocardial infarction and acute ulceration of the duodenum is generally recognized, however.

The final illustration (Fig. 6) shows the focal necrosis present in the central portions of the hepatic lobules. This lesion is often associated with myocardial infarction but can occur in its absence when acute passive congestion is present, regardless of the cause of the myocardial failure. Microscopic sections of other organs added little more information. There was slight bronchopneumonia in the lungs and a few microscopic infarcts in the spleen, which were not unexpected in view of the extensive mural thrombus in the heart.

In summary, this patient had advanced arteriosclerosis of the coronary arteries without evidence of anatomic damage to the myocardium until a thrombosis six days before his death resulted in a very extensive infarct of the interventricular septum, wall of the left ventricle and left atrium. The clinical history correlated well in that angina was present for only three weeks. About three or four days before death acute ulcers developed in the duodenum and perforation of one led to peritonitis, the symptoms of which dominated the terminal course. The myocardial infarct involved the entire thickness of the ventricular wall and it seems likely that myocardial rupture was incipient when the patient died.

Anatomic Diagnoses: Arteriosclerosis of the coronary arteries, advanced; recent thrombus in the descending branch of the left coronary artery with mural hemorrhage; recent myocardial infarct involving the anterior portion of the interventricular septum, left ventricle and left atrium; multiple ulcers of the duodenum with a single perforation; fibrinous peritonitis with bile-stained fluid.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

* Cushing, E. H., Feil, H. S., Stanton, E. J. and Wartman, W. B. Infarction of the cardiac auricles. *Brit. Heart J.*, 4: 17, 1942.

† Harkins, H. N. Acute ulcer of the duodenum (Curling's ulcer) as a complication of burns; relation to sepsis. *Surgery*, 3: 608, 1938.

Special Feature

Abstracts of Papers Presented at the National Meeting Held in Atlantic City, May 2, 1950

STUDIES OF THE ANTIDIURESIS OF QUIET STANDING. *Franklin H. Epstein, M.D., Allan V. N. Goodyer, M.D., F. Douglas Lawrason, M.D.* and *Arnold S. Relman, M.D., Boston, Mass.* (From the Dept. of Internal Medicine, Yale University School of Medicine, New Haven, Conn., and the Evans Memorial, Massachusetts Memorial Hospitals, Boston, Mass.)

When a man stands motionless, the plasma volume contracts and the load of sodium delivered to the renal tubules decreases because of a decline in the rate of glomerular filtration; simultaneously, the rates of excretion of salt and water diminish. The relationships of these events were studied in experiments in which serum albumin and hypertonic saline were infused during quiet standing. Infusions of hyperosmotic (25 per cent) and isosmotic (4 per cent) albumin prevented the contraction of plasma volume during standing. Nevertheless urine volume, sodium excretion, glomerular filtration rate (mannitol), renal plasma flow and the ratio of sodium excreted to sodium filtered (E_{Na}/F_{Na}) all decreased. In five experiments, although infusion of 400 cc. of hypertonic saline (3 to 6 per cent) increased the concentration of sodium in the serum 4 to 12 mEq./L.), the rate of sodium filtration declined. In these five subjects sodium excretion and E_{Na}/F_{Na} increased in two in whom the fall in glomerular filtration rate and filtered sodium was slight. In another, despite a significant decline in sodium filtration, E_{Na}/F_{Na} increased although sodium excretion fell. In the remaining two subjects glomerular filtration rate, filtered sodium, E_{Na}/F_{Na}, and sodium excretion all decreased.

These data suggest that the antidiuresis and fall in glomerular filtration rate and renal plasma flow associated with quiet standing are not dependent upon contraction of the total plasma volume. During quiet standing infusion of hypertonic saline may increase sodium excretion without increasing the load of filtered sodium presented to the tubules. It appears that under the conditions of these experiments the renal response to hypertonic saline is not entirely dependent on increase in the rate of sodium filtration.

EFFECT OF DIGOXIN ON SODIUM EXCRETION. *S. J. Farber, M.D., E. D. Pellegrino, M.D., J. D. Alexander, M.D. and D. P. Earle, M.D., New York, N. Y.* (From the Dept. of Medicine, New York University College of Medicine.)

Intravenous digoxin in congestive heart failure caused prompt increase in water and sodium excreted. In ten observations sodium excretion increases averaged 154, range 27 to 624 microequivalents/minute. In half there was no change in glomerular filtration rate (GFR) while in others increases ranged from 10 to 17 ml./minute. Renal plasma flows and filtration fractions changed little. Venous pressure declined in all. In a severely hyponatremic patient digoxin caused diuresis with increased potassium rather than sodium excretion. In five instances in which cardiac output was measured sodium excretion was not related to cardiac output.

In five patients with cirrhosis and ascites and in two with nephrotic edema, average control sodium excretion values were 16 microequivalents/minute before and 39 after digoxin.

Digoxin was given to twenty-one non-edematous subjects. There was no increase in sodium excretion in five subjects, equivocal changes in two but in the remaining 14 increases ranged from 28 to 114 microequivalents/minute. The control value for the group was 108 microequivalents/minute, increasing to 141 after digoxin. At corresponding times in eleven subjects not given digoxin sodium excretions were 102 and 101 microequivalents/minute. Venous pressure measured in four subjects changed little. Digoxin appears to exert a direct

tubular action in non-cardiac subjects. The drug causes much greater excretion of sodium in patients with congestive heart failure along with decreasing venous pressure but this is not necessarily related to changes in cardiac output or in glomerular dynamics.

TISSUE ANALYSES SHOWING POTASSIUM DEPLETION IN NEPHROSIS. *C. L. Fox, Jr., M.D. and (by invitation) L. B. Slobody, M.D., New York, N. Y.* (From the Dept. of Bacteriology, College of Physicians and Surgeons, Columbia University and Dept. of Pediatrics, New York Medical College.)

Previous studies of the nephrotic syndrome have revealed extracellular hypotonicity, acidosis and hyperpotassuria. To investigate the intracellular compartment, analyses were made of skeletal muscle and organs obtained from six children who died with nassive nephrotic edema. (Sodium lactate and potassium acetate had been administered in varying amounts to each patient in the effort to correct prevailing electrolyte abnormalities.) Control tissues were obtained from presumably well children dying suddenly. Analyses were performed for water, Na, K, Cl, P, protein and non-protein nitrogen. The results are expressed in terms of dry weight, i.e., cell solids for comparison with non-edematous tissues. Potassium was decreased from the control range (440–450 mEq./kg. dry weight) to 137–350 mEq. In contrast, phosphate was but slightly reduced. Sodium, chloride and water were markedly increased. The reduction in muscle potassium may in part represent exchange with the increased sodium but the large amount of chloride present suggests that most of the Na occurred with Cl and water in the massive edema.

Although biopsy material from patients with no prior electrolyte administration is essential, the data indicate an extreme state of potassium depletion and also call attention to the profound changes in intracellular composition in this syndrome.

HYPONATREMIA IN PORTAL CIRRHOSIS WITH ASCITES. *William P. Nelson III, M.D., Jack D. Rosenbaum, M.D. and Maurice B. Strauss, M.D. Framingham, Mass.* (From the Medical Service, Cushing Veterans Administration Hospital.)

Therapeutic success of sodium restriction in edema depends upon the gain or loss of sodium and extracellular water in physiologically equivalent proportions. Hyponatremia occurs most frequently with reduced extracellular fluid volume and total extracellular sodium content. Fall in concentration despite retention of extracellular sodium has been recognized occasionally, but its mechanisms are obscure. It has not been previously emphasized in cases of portal cirrhosis with ascites. In a patient with ascites but with no edema, who required repeated paracentesis, it was possible to study the pathogenesis of severe symptomatic hyponatremia.

Studies of water and electrolyte balance, serum protein and electrolytes, hemoglobin and hematocrit demonstrated the following events after paracentesis: (1) Ascites reaccumulated rapidly despite stringent restriction of sodium intake with free access to water. (2) External losses of sodium were negligible, but retention of water in excess of sodium resulted in progressive hyponatremia with oliguria, hemoconcentration, circulatory shock, nitrogen retention and mental confusion. (3) These manifestations were corrected by administration of hypertonic saline, and were prevented when the fluid intake was almost exclusively isotonic saline. (4) However, when salt intake was liberal ascites formed most rapidly. Apparently ascites formation was obligatory. When water without the required electrolyte was supplied, hyponatremia and hypotonicity developed despite excess total extracellular fluid volume resulting in a syndrome indistinguishable from that seen when hyponatremia occurrs with decreased extracellular fluid volume. With segregation of a portion of the extracellular fluid in the abdomen, it is suggested that the "effective" extracellular fluid volume of the rest of the body was critically decreased.

HEMOLYTIC TRANSFUSION REACTIONS DUE TO USE OF DANGEROUS UNIVERSAL DONORS. *Richard M. Christian, M.D., Donald M. Ervin, M.D. (by invitation) and Lawrence E. Young, M.D. Rochester, N. Y.* (From the Dept. of Medicine, University of Rochester School of Medicine and Dentistry.)

Four hemolytic reactions resulting from transfusion of group 0 whole blood or plasma into group A recipients have been observed. In each instance there was prolonged destruction of the recipient's erythrocytes as evidenced by the development of anemia, spherocytosis and

increased osmotic and mechanical fragility of the red cells persisting for a number of days following the transfusions. In one case 10 ml. of a commercial preparation of soluble A and B factors added to the group 0 whole blood did not prevent but may have lessened the hemolytic reaction.

The alpha antibodies in the plasma of the dangerous group 0 donors had characteristics usually ascribed to immune antibodies; they fixed complement, acted as hemolysins, were difficult to neutralize with soluble A and B factors, were capable of giving a positive Coombs test, and their ability to agglutinate cells was enhanced by the presence of normal human serum. The hemolysin titer of immune alpha antibodies was reduced more readily by soluble A factor than was the agglutinin titer. The anti-A titer of these sera varied from 1:320 to 1:10,240 using saline as a diluent. None of the donors had been given a transfusion of blood or plasma or had had a heterospecific pregnancy.

Twelve of 100 random group 0 sera, after neutralization with soluble A and B factors, produced indirect Coombs tests with A_1 cells and agglutinated A_1 cells suspended in compatible normal human serum. These tests were most sensitive in detecting small amounts of immune alpha antibody in group 0 serum and are therefore proposed as screening procedures for elimination of dangerous universal donors.

EFFECTS OF BANTHINE ON GASTRIC SECRETIONS AND GASTROINTESTINAL MOTILITY IN MAN. *C. Keith Lyons, M.D. (by invitation) and Keith S. Grimson, M.D., Durham, N. C.* (From the Dept. of Surgery, Duke University School of Medicine.)

Banthine, a quaternary ammonium compound (beta-diethylaminoethyl xanthine 9-carboxylate methobromide or chloride), has been tested in 120 patients studying effects of 100 or 200 mg. by intravenous, intramuscular or oral administration and comparing effects with those of atropine or Dibutoline. As judged by gastrometric balloon methods and by roentgenographic study, Banthine given intramuscularly eliminated or effected a marked reduction of peristalsis lasting several hours. Atropine intravenously or intramuscularly produced a less consistent reduction lasting about an hour but Dibutoline effected for an hour as complete a cessation of activity as Banthine. Banthine given orally produced marked reduction or elimination of peristalsis lasting several hours; whereas atropine orally effected only slight temporary changes and Dibutoline orally was not effective.

Effect on gastric secretions of each drug by each route of administration was also determined. Results were variable. Banthine effected more frequent, more pronounced and longer lasting reduction of volume and acidity than atropine or Dibutoline (i.v. or i.m.). With oral administration Banthine was effective, atropine had a variable effect and Dibutoline no effect. During the period of reduction of free acid an hour or more after Banthine, 100 mg. or with greater consistency 200 mg., insulin hypoglycemia failed to produce high acid in some patients, elevation occurring in others.

EPIDEMIC OF Q FEVER AMONG EMPLOYEES OF A RENDERING PLANT. *Harry A. Feldman, M.D., A. Clement Silverman, M.D. and Charles V. Adair, M.D., Syracuse, N. Y.* (From the Dept. of Medicine of the Syracuse University College of Medicine and the Communicable Disease Division of the Syracuse Health Department.)

In October 1949 several employees of a Syracuse, New York, rendering company were ill with a disease suggestive of Q fever. In retrospect the first patient had become ill on September 16th; the last man became sick on December 7th. Complement-fixation tests were performed on the sera of 86 of the 130 (an inconstant number) people employed at this plant. Titers of 1:40 or greater were present in thirty-three while two were positive at 1:20. Definite antecedent illnesses had occurred in thirty of the thirty-five, whereas the remaining five were detected during a serologic survey of the plant personnel. The clinical manifestations among serologically proven cases ranged from very slight to severe illnesses. Only nine of the patients were hospitalized and these were distributed among five different hospitals. Clinical diagnoses included upper respiratory infection, atypical pneumonia, typhoid fever and miliary tuberculosis. Treatment regimens varied from none for six individuals to different combinations of antibacterial substances. Five men received aureomycin only and responded rapidly to this therapeutic agent. Five others received aureomycin after failing to respond to other therapeutic agents, and the disease seemed to be interrupted abruptly by the aureomycin. One patient received chloramphenicol after failing

to respond to sulfadiazine and penicillin, while another received chloramphenicol after responding to, but developing nausea with, aureomycin. Variations in clinical manifestations, as well as the reaction to different forms of therapy will be demonstrated. Evidence will be presented which suggests that this epidemic of Q fever, a disease hitherto not detected in this part of the country, could have been induced by Q-infected guinea pig carcasses discarded with other experimental animals and shipped to this rendering plant from a research institution not located in Syracuse.

EXPERIMENTAL AND CLINICAL STUDIES WITH HEXAMETHONIUM (C6). *Frank Finnerty, Jr., M.D. and Edward D. Freis, M.D., Washington, D. C.*

Recently a homologous series of polymethylene-bis-trimethyl ammonium compounds has been found in animals to block transmission through autonomic ganglia. One of these, hexamethonium (C6), has been studied for the first time in man. After intravenous administration of 40 to 60 mg. of active substance there was a fall in the supine blood pressure in fifteen of the eighteen patients studied varying from 0.5 to 24 per cent of the mean arterial pressure. This was accompanied by postural hypotension in all patients with collapse in two-thirds of the group on standing. In addition, there was marked inhibition of sympathetic reflexes including (1) abolition of the vasopressor overshoot following the Valsalva maneuver, (2) complete abolition of the cold-pressor response in four of six patients and (3) marked hypotension after congesting the limbs. Digital plethysmography disclosed increase in pulse volume and marked increase in digital blood flow both in normal subjects and patients with vasospastic diseases. In both moderate and cool environments the skin temperature of the toes in the normal limbs usually rose 15 to 20° with abolition of the temperature gradient.

There were no side effects except moderate blurring of vision and postural hypotension, effects due directly to the sympatholytic action of the drug. C6 seemed much superior to TEA since (1) the duration of action was at least four times greater, (2) side effects such as tingling of the skin and palpitation were absent, (3) compensatory tachycardia was less and (4) increase in digital skin temperature was considerably more marked and prolonged. The drug appears to have a place, therefore, in the evaluation and treatment of peripheral vascular disease.

CEREBRAL CIRCULATION AND OXYGEN CONSUMPTION IN UREMIA. *A. Heyman, M.D., J. L. Patterson, Jr., M.D. and R. W. Jones, Jr., M.D., Atlanta, Ga.* (From the Depts. of Medicine and Physiology, Emory University School of Medicine, and Grady Memorial Hospital.)

The cerebral blood flow (CBF), oxygen consumption ($CMRO_2$) and vascular resistance (CVR) of the brain in uremia have been determined by the nitrous oxide technic in fourteen patients and in sixteen control subjects. The mean CBF in five patients with pyelonephritis was normal, but the $CMRO_2$ was diminished to a low value of 1.95 cc./100 gm. brain/min., representing a reduction of 37 per cent. The mean blood pressure and the CVR were only slightly elevated. In contrast, nine patients who had malignant nephrosclerosis or glomerulonephritis showed a definite reduction in the mean CBF, with a value of 45 cc./100 gm. brain/min. The mean arterial pressure and CVR were both markedly elevated. The $CMRO_2$ in this group was reduced to the same degree as in the patients with pyelonephritis. The NPN in these two groups was comparable with a mean value of 177 and 158 mg. per cent, respectively. The differences in the CBF in these two groups of patients were probably caused by different degrees of cerebral vascular disease or by the increase in intracranial pressure which exists in malignant hypertension.

The degree of reduction in $CMRO_2$ correlated fairly well with the degree of mental deterioration of the patient but correlated poorly with the level of the NPN. As the patient improved or became worse the value for $CMRO_2$ increased or diminished, respectively. The average basal metabolic rate in seven patients was normal while the mean $CMRO_2$ was only 64 per cent of normal. This suggests that uremia has a greater effect on the brain than on most body tissues.

Since the patients with pyelonephritis showed little evidence of cerebral vascular disease but a striking reduction in $CMRO_2$, it is suggested that changes in extracellular fluid alone are capable of producing alterations in cerebral metabolism in uremia.

PATHOGENESIS OF PULMONARY EDEMA IN MITRAL STENOSIS. *Richard Gorlin, M.D., Florence W. Haynes, M.D. and Lewis Dexter, M.D., Boston, Mass.* (From the Medical Clinic, Peter Bent Brigham Hospital, and the Dept. of Medicine, Harvard Medical School.)

Seven studies have been made by cardiac catheterization in six patients with mitral stenosis at rest and during exercise. Cardiac outputs were estimated by the direct Fick method; peripheral arterial and mean pulmonary "capillary" pressures ("PC") were recorded. Assuming "PC" pressure to approximate left atrial mean pressure, left ventricular diastolic pressure to equal 5 mm. Hg and deriving the diastolic filling period per minute from arterial pressure tracings, the rate of mitral valvular blood flow (MVF) in cc/sec. was calculated:

$$\frac{\text{Cardiac output (cc./min.)}}{\text{Diastolic filling period per minute (sec./min.)}}$$

The cross sectional area (MVA) of the mitral valve was calculated according to the equation:

$$\frac{\text{MVF}}{0.7\sqrt{2g(\text{"PC"} - 5)}}$$

Significant elevations in cardiac output occurred in three of the seven patients on exercise. In six of the seven increases in pulse rate or systolic ejection period occurred with significant decreases in diastolic filling time per minute. Whether due to increase in minute output or to decrease in diastolic filling time per minute, the rate of mitral valvular flow increased and was associated with a marked rise in "PC" pressure. The smaller the valve cross sectional area, the higher the rise in pressure for a given increase in rate of flow.

Pulmonary edema on exercise was seen in those with high resting "PC" pressures who developed marked rises in pressure for only small increases in rate of flow. The occurrence of pulmonary edema is closely correlated with the degree and duration of elevation of "PC" pressure, which in turn is directly related to MVA and MVF, the latter being increased by tachycardia, increased systolic ejection period and increased cardiac output.

COR PULMONALE. AN EXPERIMENTAL STUDY UTILIZING A SPECIAL CARDIAC CATHETER. *Charles T. Dotter, M.D. and Daniel S. Lukas, M.D., New York, N. Y.* (From the Depts. of Radiology and Medicine, New York Hospital-Cornell Medical Center. This investigation was supported by a grant from the New York Heart Association.)

Although several experimental studies of the problem have been previously reported, the alterations in hemodynamic pattern that occur in acute cor pulmonale remain poorly defined. Employing a specially designed double-lumen cardiac catheter with an inflatable balloon near its tip, acute cor pulmonale can be induced in the intact experimental animal by sudden closure of the left or right branch of the pulmonary artery. The standard electrocardiographic limb leads and right heart pressures have been recorded simultaneously during such closure in dogs anesthetized with intravenous pentabarbital and striking changes encountered. In fourteen trials in which pulmonary artery obstruction was maintained for an average of three minutes, the right ventricular systolic pressure rose rapidly from an average control level of 23 mm. Hg to 64 mm. Hg with an accompanying elevation of the end-diastolic or ventricular filling pressure of from 2 to 8 mm. Hg. In six experiments the right ventricular hypertension was maintained until obstruction was terminated. In the other eight experiments right ventricular failure characterized by further elevation of the diastolic pressure to abnormal levels and a declining ventricular pulse pressure occurred during the course of the vascular obstruction. In the latter series of experiments the relationship of right ventricular filling pressure to ventricular pulse pressure was found to obey Starling's Law. Systemic arterial pressure, measured in six experiments, fell following pulmonary arterial obstruction; in three instances marked systemic hypotension persisted for the duration of the obstruction. Despite the development of marked right ventricular hypertension, no appreciable change in electrical axis occurred. Electrocardiographic changes consisted of lowering and inversion of the T waves and depression of the RS-T segments. These were interpreted as representing myocardial ischemia. Abnormal rhythms appeared during advanced right ventricular failure.

Possible factors in the genesis of right ventricular hypertension in this study and further uses of the modified catheter in physiologic investigation are discussed.

DYNAMICS OF EXPERIMENTAL ATRIAL SEPTAL DEFECT. *James W. Dow, M.D. and James V. Maloney, M.D., Boston, Mass.* (From the Dept. of Pediatrics, Children's Medical Center; the Dept. of Physiology, Harvard School of Public Health; and the Dept. of Pediatrics, Harvard Medical School.)

Cardiac outputs were measured by the direct Fick method and pressures by Sanborn electromanometer through catheters passed by way of the venous system into the chambers of the right hearts, and retrograde through a peripheral artery into the left ventricles and atria of dogs anesthetized with nembutal. Control observations were made before any procedure was undertaken, and subsequently some weeks after operative atrial defects were created by the Blalock technic. In a few dogs the acute effects of an operative defect were observed. Except in some of the acute experiments all observations were made with the chest closed and during spontaneous respiration.

Atrial mean approximated ventricular diastolic pressures in both sides of the heart. Before operation left atrial mean and left ventricular diastolic pressures exceeded right atrial mean and right ventricular diastolic pressures by from 1 to 4 mm. of Hg. After the atria were placed in communication the difference between these left and right ventricular filling pressures was reduced when the defect created was small, disappeared entirely when the defect was large. The common atrial pressure with the defect open tended to approximate right atrial pressure in the control observations. Right ventricular outputs and stroke volumes were greater; left ventricular outputs and stroke volumes were apparently less than in the control state.

Since the two ventricles fill to equal volumes at different pressures while the septa are intact, it is apparent that the volume-pressure characteristics of the ventricles are dissimilar, and that the right ventricle is more readily distensible than the left. When a large defect is created, a pressure difference cannot be maintained between the atria and the two ventricles are constrained to fill from a common chamber at equal pressure. Under these conditions the more readily distensible right ventricle fills to a greater volume than the left ventricle. The unequal filling of the two ventricles from a common pressure source, rather than maintenance of an interatrial pressure gradient, accounts for the left to right shunting that is characteristic.

CHANGES IN RESPONSIVENESS TO INSULIN IN DIABETES MELLITUS INDUCED BY DESOXYCORTICOSTERONE. *Hyman J. Zimmerman, M.D., Alvin E. Parrish, M.D. (by invitation), and Louis K. Alpert, M.D., Washington, D. C.* (From the Veterans Administration Hosp. and George Washington Univ. School of Medicine.)

Previous study of a group of patients with diabetes in whom liver biopsies were performed revealed a high degree of correlation between fatty infiltration of the liver and insulin insensitivity. Although the insulin insensitivity might have been due to the fatty infiltration, other data made it seem more likely that the two phenomena had a common cause. The development of fatty livers and insulin insensitivity which has been demonstrated following the administration of anterior pituitary extracts in animals suggested the possibility that the factor operating in the insulin-insensitive human diabetic might also be of pituitary origin. The demonstration by Sayers and his co-workers of the ability of desoxycorticosterone to increase insulin sensitivity in rats, presumably through inhibition of the output of ACTH, led to our investigation of the effect of this steroid on insulin sensitivity in diabetes with the use of the Himsworth glucose-insulin tolerance test.

In nine insulin-insensitive diabetics and in six who were sensitive to insulin the effects of the administration of desoxycorticosterone for periods of four to ten days on the glucose-insulin tolerance curve, fasting blood sugar and glycosuria were studied. In eight of the nine patients who were insensitive to insulin the glucose-insulin tolerance test was changed from the insensitive to the sensitive type. In the remaining one there was a slight and much less definite increase in sensitivity. After discontinuation of desoxycorticosterone reversion of the glucose-insulin tolerance test to the insensitive type usually occurred in one to three weeks. Of the six patients who were previously sensitive to insulin, none showed any increase in sensitivity after administration of desoxycorticosterone, in fact the glucose-insulin tolerance test in four of the patients showed some decrease in sensitivity.

The difference in response to desoxycorticosterone of those patients who are insensitive to insulin and frequently show fatty livers, and those who are sensitive to insulin and in whom

fatty livers are rare, is additional supporting evidence that insulin-sensitive diabetes probably is of pancreatic origin, while insulin-insensitive diabetes is due at least in part to a pituitary factor.

HYPERCALCEMIA, HYPOPHOSPHATEMIA AND SALT LOSS CAUSED BY THIOCYANATE. *Richard Gubner, M.D., Brooklyn, N. Y.* (From the Medical Department, Equitable Life Assurance Society of the United States, and the Dept. of Medicine, State University of New York College of Medicine.)

Subjects with hypertension given thiocyanate even when blood levels are maintained below 12 mg. per cent not infrequently develop side reactions, notably sluggishness, muscular weakness and gastrointestinal symptoms. The present study suggests that these symptoms are due to hypercalcemia and hypophosphatemia associated with renal loss of electrolytes, i.e., phosphate, calcium and sodium chloride.

In five of six subjects with normal renal function whose average thiocyanate blood level was 8.2 mg. per cent the Robinson-Power-Kepler test of urinary salt loss was abnormal. Adrenal function, as studied by the eosinophile response to epinephrine, was normal (average initial eosinophile count 177/mm³, average fall three hours after 0.5 mg. epinephrine, 57 per cent). There is no evidence therefore that thiocyanate produces adrenal insufficiency. Thiocyanate specifically inhibits carbonic anhydrase, which is responsible for renal tubular acidification of urine and conservation of sodium, and its effect in causing salt loss is probably due to inhibition of carbonic anhydrase, as is the case with sulfanilamide.

In eight subjects receiving thiocyanate for periods varying from four weeks to eight years, with an average blood level of 8.15 mg. per cent, the serum calcium was uniformly elevated (average 13.2 mg. per cent, highest 15.2 mg. per cent), and the blood phosphorus was significantly lowered (average 2.8 mg. per cent, lowest 2.1 mg. per cent). The Sulkowitch test for urine calcium was highly positive in all these subjects. These electrolyte changes as well as the symptoms produced by thiocyanate resemble those occurring in hyperparathyroidism and it appears that the action of thiocyanate on the renal tubule is similar to that of the parathyroid hormone. Osteoporosis has been reported in subects receiving thiocyanate for sustained periods.

It is suggested that the electrolyte changes produced by thiocyanate may have therapeutic application when it is desired to produce salt loss or to elevate blood calcium.

EFFECT OF EXOGENOUS THYROID HORMONE ON THYROID FUNCTION OF NORMAL HUMAN SUBJECTS AS DETERMINED WITH RADIOACTIVE IODINE. *Monte A. Greer, M.D., Boston, Mass.*

Although it has been known for many years that a reciprocal relationship appears to exist between the levels of circulating thyroid hormone and pituitary thyrotrophin, until recently a direct estimation of thyroid activity in man was not feasible. A study was made of the thyroid function of over thirty normal human subjects by following the rate of accumulation in the thyroid gland of an administered dose of radioactive iodine by means of serial counts with an externally placed shielded Geiger counter. Following control studies the subjects were given graded daily doses of desiccated thyroid and determinations of their thyroid activity were repeated at intervals of a few days to several months.

The accumulation of I^{131} by the thyroid glands of all subjects was suppressed within a few days by the administration of sufficient exogenous hormone to the levels seen in myxedema. The amount of U.S.P. desiccated thyroid required to produce this suppression varied from 60 to 180 mg. per day.

This study is interpreted as demonstrating that the administration of physiologic amounts of exogenous thyroid to normal human subjects results in a decrease in the function of the subject's own thyroid gland equivalent to the dosage of the exogenous thyroid administered. The subject will maintain a stable euthyroid level of circulating thyroxine unless toxic amounts of exogenous hormone are administered.

STUDIES ON THE PRECIPITATION OF CEREBROSPINAL FLUID PROTEINS BY ZINC SULFATE. *Alfred M. Donovan, M.D., Joseph M. Foley, M.D. and William C. Moloney, M.D., Boston, Mass.* (From the Clinical Research Laboratory of the First and Third Medical Services and the Neurological Unit, Boston City Hospital.)

Abnormalities of protein fractions in the cerebrospinal fluid are known to occur in certain neurologic disorders but their demonstration in the routine clinical laboratory has been re-

stricted to the Pandy test and colloidal reactions. Most significance has been attached to the colloidal gold reaction, which is difficult to standardize, cumbersome to perform and occasionally confusing to interpret. A simple precipitation test is described which avoids the difficulties of the colloidal gold technic and correlates more effectively with those disorders in which one would expect an abnormality of protein fractions. The test is performed by adding to 1 cc. of spinal fluid 1 cc. of a solution of 0.005 molar zinc sulfate buffered to a pH of 7.1 by a barbital system. At the end of twelve to eighteen hours the degree of precipitation is read on a 0 to 4+ basis. Two or more plus is considered significant. Over 300 spinal fluids were examined. The presence of white blood cells alone had no influence on the reaction, but red blood cells in large numbers were almost always associated with a precipitation. No correlation could be established with the Pandy test. A total protein of over 75 mg./100 cc. was likely to be associated with a significant zinc reaction. The highest correlation was with the colloidal gold reaction, the presence of a 3 or higher in the gold curve being associated almost always with a significant zinc precipitation. The discrepancies which occurred showed far fewer "false positives" in the zinc reaction.

In nineteen cases labelled multiple sclerosis the zinc test was significant in seventeen. In the two exceptions this diagnosis was considered to be only tentative. In twenty cases in which the spinal fluid Hinton or Wassermann was positive, the zinc test corresponded completely with the colloidal gold. In sixty-six cases of an assorted group of chronic alcoholics, epileptics and senile psychotics the zinc test was significant only once while the colloidal gold gave eight "false positive" reactions.

SYNERGISTIC ACTION OF COMBINATIONS OF THE ANTIBIOTICS AND THEIR PRACTICAL APPLICATION. *M. J. Romansky, M.D.; M. Fusillo, B.S. and M. Levy, B.A., Washington, D. C.* (From the Dept. of Medicine, George Washington University School of Medicine and the Antibiotic Laboratory, Walter Reed General Hospital.)

In recent years it has become obvious by *in vitro* studies that certain bacteria have developed a resistance to penicillin and streptomycin. A comparison between 1947 and 1949 of the *in vitro* sensitivity of a large number of strains of bacteria shows an increase in resistance of certain of these. The percentage of increase to penicillin has varied between 10 and 44 per cent and to streptomycin between 8 to 64 per cent. In addition, contrary to early reports, our clinical studies indicate that certain bacteria have developed resistance *in vivo* to aureomycin and chloramphenicol in a fairly short time.

We have carried out *in vitro* as well as clinical studies with combinations of the antibiotics. These have included penicillin, streptomycin, aureomycin and chloramphenicol. The combination of aureomycin and chloramphenicol shows a synergistic effect against 43 to 92 per cent of the gram-positive organisms. This combination also showed a synergistic effect against 60 to 87.5 per cent of the gram-negative ones. Penicillin and aureomycin evidenced a synergistic effect against 59 to 100 per cent of the gram-positive organisms and 0 to 75 per cent of the gram-positive organisms were affected in the same fashion by penicillin and chloramphenicol. A synergistic effect was also noted against 37 to 90 per cent of the gram-positive organisms by penicillin and streptomycin. Utilizing streptomycin and aureomycin 40 to 91 per cent of the gram-negative bacteria were affected synergistically and with streptomycin and chloramphenicol 44 to 100 per cent showed this phenomenon. Of particular interest is the increasing synergistic effect as an organism develops resistance.

We are not suggesting from these studies that all infections should be treated with various combinations of antibiotics. Certain of these due to the proteus, pseudomonas, streptococcus fecalis and hemolytic staphylococcus aureus warrant a combination. Because of this synergistic action the combinations are indicated in infections which do not respond to a course of a single antibiotic. This procedure is particularly applicable to subacute bacterial endocarditis when the organism is relatively resistant to penicillin or the other antibiotics individually.

EFFECT OF PENICILLIN AND AUREOMYCIN ON THE NATURAL COURSE OF STREPTOCOCCAL PHARYNGITIS AND TONSILLITIS. *Capt. Lewis W. Wannamaker, M.C., AUS, Capt. William R. Brink, M.C., AUS, Capt. Floyd W. Denny, M.C., AUS, Wyoming, and Charles H. Rammelkamp, Jr., M.D., Cleveland, Ohio.* (From the Streptococcal Disease Laboratory, Francis E. Warren Air Force Base, and the Dept. of Preventive Medicine, Western Reserve University.)

A group of 475 patients with streptococcal exudative tonsillitis or pharyngitis was studied by clinical, bacteriologic and serologic methods to determine the effectiveness of penicillin and aureomycin on the natural course of this disease. There were 198 patients who received no treatment, 197 received 1,200,000 units of procaine penicillin G in peanut oil over a four-day period, and eighty were treated with 8.5 gm. of aureomycin over a similar period. Both penicillin and aureomycin therapy shortened the febrile temperature curve and resulted in a more rapid disappearance of abnormal symptoms than occurred in the control group. Aureomycin was more effective than penicillin although the differences were not marked. Treatment instituted within the first twenty-four hours of illness resulted in a more rapid recovery than when therapy was delayed. There was no striking improvement in physical signs following penicillin or aureomycin therapy although in almost every instance the physical signs in patients receiving treatment remitted more rapidly than in control patients.

Suppurative complications were unusual in all groups. Seven patients subsequently developed acute rheumatic fever. Five of these were from the control group and two were from the penicillin-treated group.

The total leukocyte count decreased more rapidly in the treated groups than in the control patients. In contrast to penicillin, aureomycin therapy did not result in the permanent eradication of the carrier state. Both penicillin and aureomycin therapy inhibited the production of antistreptolysin "O."

USE OF TERRAMYCIN IN SOME INFECTIOUS DISEASES. *E. R. Caldwell, Jr., M.D., H. W. Spies, M.D., C. K. Wolf, M.D., M. H. Lepper, M.D., R. L. Whelton, M.D. and Harry F. Dowling, M.D., Washington, D. C.*

Terramycin has been used in the treatment of seventy-six patients. Twenty of these patients had a characteristic bacterial pneumonia. Sputum examination for pneumococci was positive in seven and negative in thirteen. Three patients had pneumococcic bacteremia. There were two deaths in this group. One was an eighty-five-year old woman with bacteremia who improved from her infection but died in heart failure on the ninth day of therapy. The second patient was a sixty-two year old alcoholic who made an initial response but relapsed after failing to take the drug by mouth. Intravenous therapy was started, but he exhibited lobar pneumonia, advanced cirrhosis and an ulcerative lesion with perforation of the colon at autopsy. Ten patients with urinary tract infections caused by gram-negative rods did well clinically and had negative follow-up cultures. Another patient who had a pseudomonas pyelonephritis improved but the urine cultures became positive for proteus. Four patients with postpartum endometritis caused by gram-negative rods rapidly recovered, as did seven patients with gonococcal urethritis. Twelve patients with measles responded rapidly but the response could not be evaluated. Five patients with mumps seemed not to be benefited. One typhoid carrier with positive duodenal drainages was treated for one week prior to cholecystectomy at which time the gallbladder bile was sterile. Three patients with pharyngitis, one with beta streptococcal otitis media, three with subcutaneous infections and one with infectious mononucleosis all did well. One patient with a pseudomonas osteomyelitis of the jaw failed to improve. No major toxic reactions have been encountered. Substernal burning, nausea, vomiting or diarrhea occur. The total incidence of these complications is about 10 per cent. Vertigo and drowsiness have been a minor complaint in less than 5 per cent.

PATTERN OF "SPONTANEOUS" REMISSIONS IN LEUKEMIA OF CHILDHOOD OBSERVED IN 26 OF 300 CASES. *Louis K. Diamond, M.D. and A. Leonard Luhby, M.D., Boston, Mass.* (From the Dept. of Pediatrics, Harvard Medical School, the Infants' Hospital and Children's Medical Center.)

The incidence and pattern of "spontaneous" remissions were studied in 300 children with leukemia encountered over a twenty-five-year period. Of this group, 90 per cent had acute "blast cell" leukemia. Among these, twenty-six cases of "spontaneous" remissions, an incidence of 9.65 per cent were observed; 4.45 per cent were complete remissions, 5.2 per cent were partial. In "complete" remissions the blood, bone marrow (when examined), symptomatic and physical findings became normal. In "partial" remissions each category showed striking improvement. Complete remissions averaged ten weeks in duration, partial remissions eight weeks. Total duration of life following the onset of leukemia averaged 29.7 weeks in the children with complete, 23.6 weeks in those with partial remissions.

The disease and pattern of remission were alike in all patients in three important respects: (1) All had "blast cell" acute leukemia. Total peripheral white cell counts, with two exceptions, were normal or reduced, occasionally slightly elevated. (2) Remission was characteristically preceded by a marked leukopenia of the blood and hypoplasia of the bone marrow. (3) Severe infection preceded this "hypoplastic phase" in 92 per cent of the complete remissions, in 75 per cent of the partial remissions. Infections were pyogenic; septicemia was frequent.

Interestingly, three-fourths of the complete remissions occurred in 1945, 1946 and 1947 when, among other things, several important antibiotics became widely available. These may have prevented infections which became severe from necessarily becoming fatal. Attention is also called to the many similarities of the pattern and response of these patients to those successfully treated with aminopterin and ACTH.

THERAPEUTIC EFFECT OF AUREOMYCIN IN PERNICIOUS ANEMIA. *Herbert Lichtman, M.D. (by invitation), Victor Ginsberg, M.D. (by invitation) and Janet Watson, M.D., Brooklyn, N. Y.* (From the Dept. of Medicine, Kings County Hospital.)

An early theory of the etiology of pernicious anemia was that it is a hemolytic anemia. Dock has emphasized the importance of a possible toxic effect of the bacterial flora of the gastrointestinal tract in constitutionally predisposed individuals. It was our purpose to study the effect of sterilization, or at least alteration of the bacterial flora on the course of pernicious anemia in relapse. Preliminary studies were made on the effects of aureomycin in three cases of pernicious anemia and one case of nutritional macrocytic anemia.

In the first case of P.A., after a negative control period of ten days of 3 gamma daily orally or vitamin B12b, 3 gm. of aureomycin daily were added. This resulted in a reticulocyte peak of 12.2 per cent seventeen days later. In thirty-six days the red blood cells increased by 2.01 million/cu. mm., the hemoglobin by 8.4 gm. and the hematocrit by 25 per cent. In the second case of P.A., after a negative control period of twelve days on a diet free of animal protein plus 2 gm. of aureomycin daily, 200 gm. of chopped beef were added to the diet. This resulted in a definite hematologic response. The third case of P.A. was treated with 2 gm. of aureomycin and 2 gm. of streptomycin orally each day. A suboptimal but significant hematologic response occurred. A case of nutritional macrocytic anemia was treated with a diet free of animal protein and 2 gm. of aureomycin daily for thirteen days with no appreciable effect. Then after 3 gamma of vitamin B12b was given by mouth daily, a reticulocytosis and rise of red cells occurred. In each case the sternal marrow, which was originally megaloblastic, was converted to normoblastic.

LEUKEMIC CROSS TRANSFUSIONS IN MAN. *Howard R. Bierman, M.D., R. L. Byron, Jr., M.D., Jonathan T. Lanman, M.D., Kenneth S. Dod, M.D. and P. L. Morrow, M.D., San Francisco, Calif.* (From the Laboratory of Experimental Oncology, National Cancer Institute, National Institutes of Health, U.S. Public Health Service, and the Cancer Research Institute, University of California Medical School.)

Rapid transfusions of 9 to 120 billion leukemic leukocytes into non-leukemic subjects revealed that the leukemic leukocytes fail to appear on the arterial side of the lesser circulation. Heparinization permits leukemic cells to pass the usual removal mechanism in the lungs.

By developing a method of direct artery-to-artery cross circulation in man an attempt was made to filter out leukemic cells in leukemic patients in the lung filter of non-leukemic patients. Seven cross transfusions have been completed on volunteer patients with various neoplastic diseases. It is possible to cross transfuse 6 to 10 L. of blood per hour both to and from the donor and recipient. To date 150 L. of blood have been cross transfused within a twenty-six-hour period. Marked decreases in leukocyte counts in the leukemic patients were observed some hours *following* the cross transfusions. Leukemic skin infiltrations disappeared over night and clinical improvement was noted within an hour after the cross circulation was begun. No evidence of leukemia has been detected in any recipient. Postmortem studies showed degenerating leukocytes and absence of leukemic infiltration of the liver and spleen and bone marrow of the leukemic patients. The procedure is experimental and extreme caution must be exercised regarding blood type and Rh compatibility, non-deliberate transmission of disease and both immediate and late effects of immunologic reactions. The concept that an

impaired removal mechanism may be as important as proliferation in leukemia has been strengthened.

THE "LUPUS ERYTHEMATOSUS PHENOMENA" OF BLOOD AND BONE MARROW. MORPHOLOGIC AND SEROLOGIC OBSERVATIONS. *Lawrence Berman, M.D. (by invitation), Arnold R. Axelrod, M.D., Herbert L. Goodman, M.D. (by invitation) and Robert I. McClaughry, B.A. (by invitation), Detroit, Mich.* (From the Depts. of Pathology, Medicine and Physiology and Pharmacology, Wayne University College of Medicine.)

Recent studies of blood and bone marrow provide useful adjuncts to the diagnosis of acute disseminated lupus erythematosus. Additional modifying facts observed in the authors' material are presented for elucidation of the morphogenesis of the phenomena. A quantitative study of the incidence of the various LE phenomena indicates that the phenomena are not unique qualitative findings, as they have been observed in patients free of the disease. The practical diagnostic importance of the changes is discussed in the light of the quantitative studies.

The authors' observations support the concept that the LE cell inclusions seen in marrow films are identical with the "hematoxylin-staining bodies" (Klemperer et al.) seen in tissues of patients with the disease. Investigation of the *in vitro* test for lupus erythematosus in which plasma from LE patients is placed in contact with marrow material from normal persons or other patients yielded the following facts: (1) LE plasma contains a factor which promotes or enhances phagocytosis of nuclear masses by leukocytes from normal blood. (2) Bone marrow material from patients with various diseases reacts with varying degrees to contact with plasma from LE patients. Cells from certain patients fail to react. (3) Postmortem serum from a patient with acute disseminated lupus erythematosus gave positive diagnostic results in the *in vitro* test. (4) Cells of animal origin can be used for the *in vitro* test. (5) Activity of LE plasma resides in a factor associated with the gamma globulin factor.

ANTICOAGULANT ACTION OF PARITOL IN HUMANS. *C. W. Sorenson, M.D. and I. S. Wright, M.D., New York, N. Y.* (From the Vascular Research Laboratories, Department of Medicine, Cornell University Medical College. This work has been aided by grants from the S. H. Kress Foundation, the Lillia Babbitt Hyde Foundation, the Albert and Mary Lasker Foundation and the Hampil Fund.)

Studies have been made on the action in humans of a synthetic anticoagulant, Paritol, a polysulfuric ester of polyanhydromannuronic acid obtained as a water-soluble sodium salt. The drug has been given to thirty-two subjects. The effect on the coagulation mechanism has been followed by a modification of the Lee-White clotting time which gave an average normal value of nine minutes. The average clotting times at the indicated intervals after intravenous doses of Paritol of 5 mg./kg. were as follows: 30 minutes; C.T. 55 minutes; 2 hours: C.T. 38 minutes; 4 hours: C.T. 26 minutes; 6 hours: C.T. 20 minutes; 8 hours: C.T. 16 minutes; 10 hours: C.T. 11 minutes and 12 hours: C.T. 13 minutes.

Eleven patients with thromboembolic disease were maintained on Paritol for periods over twenty-four hours to eight days. Satisfactory prolongation of the clotting times was maintained by intravenous doses of 2 to 5 mg./kg. given every eight to twelve hours. Reactions to the drug have been observed in four cases. One of these was characterized by signs of vascular collapse. Two developed a rapid edema of the hands which lasted six to ten hours, not associated with generalized urticaria. In one patient with impaired renal function the drug produced a further rise in the blood urea nitrogen concentration.

Case Reports

Metastatic Suppurative Arthritis with Subcutaneous Emphysema Caused by Escherichia Coli*

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ACUTE suppurative arthritis may be caused by several mechanisms, namely, blood-borne infection (metastatic), direct wounds of joints and extension from neighboring areas of infection (as from an adjacent osteomyelitis). The metastatic form of suppurative arthritis is the most frequent,[1] and the causative organisms in the great majority of instances are the Staphylococcus aureus and Streptococcus hemolyticus.[2–6] Treatment of these pyogenic arthritides has improved greatly with the advent of newer antibiotics known to be effective against gram-positive organisms. Blaisdell and Harmon[7] attributed their success in treating suppurative joint disease with oral sulfathiazole to the satisfactory delivery of the drug to the joint space, the ratio of blood level to joint level being 1.0:0.65. Similarly, Balboni[8] and McAdam[9] found adequate transfer of penicillin into joint fluid when this drug was administered intramuscularly. Keefer,[10] too, has reported good response to parenteral penicillin in Staph. aureus arthritis.

Invasion of the joint space by Esch. coli is unusual and most reviews of pyogenic joint infections omit mention of this organism. Bauer, Ropes and Short[11] describe one case of Esch. coli arthritis in which the joint involvement was secondary to Esch. coli urethritis and prostatitis. In their case the joint infection responded to treatment with sulfadiazine although the urine culture remained positive for Esch. coli and non-hemolytic streptococcus. With the introduction of streptomycin,[12] a substance exhibiting antibiotic activity against gram-negative bacilli, infections caused by Esch. coli became more readily amenable to treatment. Whereas there have been many reviews and case reports of the use of streptomycin in treating Esch. coli infections of the urinary tract,[13] blood stream,[13] meninges[14] and peritoneal cavity,[15] there has been no mention of streptomycin in the treatment of arthritis produced by Esch. coli.

The following case is reported as an instance of suppurative arthritis caused by Esch. coli and non-hemolytic streptococcus with the unusual complication of gas formation in the soft tissues surrounding the joints. Although streptomycin was of no avail in eradicating the suppurative joint process, even after surgical drainage was instituted, the bacteriological and post-mortem findings serve to emphasize the importance of doing antibiotic blood levels and organism sensitivity studies during the course of treatment of severe bacterial infections.

CASE REPORT

A fifty-five year old Negro housewife was admitted to the hospital on July 28, 1947, because of nausea, vomiting, fever, malaise and generalized myalgia of five days' duration.

She had been relatively well until five days

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before admission when she awoke with generalized malaise and nausea. That evening persistent lower substernal, non-radiating pain developed which was not relieved by soda. The patient slept poorly that night, felt warm and noted generalized muscle aches, particularly in the legs and thighs. These symptoms persisted and on the following morning she vomited after breakfast. Two days before admission she noted a sharp pain in the lower right anterior chest accentuated by breathing. There was no associated cough, expectoration, hemoptysis, hoarseness, sore throat or wheezing. She had nocturia up to five times but no dysuria or urgency. The urine appeared reddish in color. There was no recent weight loss. Bowel habits remained normal. On the morning of admission she experienced a shaking chill and hospitalization was advised.

Past history revealed that she had malaria at the age of five. At nineteen polyarthritis developed which was diagnosed as rheumatic fever. At the age of 40 she had a painful, swollen right knee joint associated with jaundice. For the past ten years she noted occasional epigastric distress with belching after meals. For many years she had experienced shortness of breath on mild exertion, orthopnea, swelling of the ankles and pain in the calves on walking.

Physical examination revealed a moderately obese, acutely ill, colored female who complained of headache and pains in the muscles of her legs and lower back. The scleras were clear; there was a marked arcus senilis bilaterally; fundoscopic examination was negative. Depressed breath sounds and a few fine crepitant rales were present at the base of the right lung posteriorly. A soft, blowing, apical systolic murmur was heard and not transmitted. The abdomen was diffusely tender, most marked in both upper quadrants. The liver and spleen were not palpable. Moderate bilateral costovertebral angle tenderness was elicited. There was mild bilateral calf tenderness but no peripheral edema. Homans' sign was negative. Examination of the joints was negative. Pelvic and rectal examinations were normal.

The temperature was 100.6°F., pulse 88, respirations 20 and blood pressure 88/58. Examination of the blood revealed a red cell count of 3,210,000 with a hemoglobin of 7.8 gm. per cent and a white cell count of 10,500 with 75 per cent neutrophils and 25 per cent lymphocytes. The urine was cloudy, had a specific gravity of 1.005, contained 2 plus albumin, no sugar, and ten to fifteen white cells per high power field on a centrifuged specimen. The erythrocyte sedimentation rate was 34 mm. per hour (Wintrobe, corrected). The hematocrit was 30. The blood Kahn reaction was negative. The blood urea nitrogen was 22 mg. per 100 cc. Chest film taken on entry was interpreted as "pneumonitis at both bases." Electrocardiogram was normal. Cervical smear for Neisseria organisms was negative. Her blood type was group "O," Rh positive. The stool was guaiac-negative and no ova or parasites were noted.

During the next two days she continued to complain of headache, nausea and generalized myalgia. Her temperature rose to 104°F., and the white cell count at this time was 9,250. Blood smear revealed no abnormal white cells. The red cells showed marked anisocytosis with slight hypochromia. The color index was 0.82; there were 404,000 platelets per cu. mm.; the reticulocyte count was 2 per cent. A sickle cell preparation was markedly positive within two hours. Blood culture was sterile. The urine contained no Bence-Jones protein. Venous pressure was 9 cm. of water.

On the evening of the fourth hospital day she experienced a shaking chill and diffuse abdominal pain. Examination revealed a temperature of 107°F., crepitant rales at the right lung base, a diffusely tender abdomen without spasm and tenderness in the calves and over the tibias. Homans' sign was negative. The white blood count at this time was 5,500 with a normal differential. A blood culture drawn at the height of her fever was negative as was a smear for malaria.

The following morning she vomited and complained of severe pain in the bones of her legs. Her temperature fell to 101°F. Rales persisted at the right lung base. A non-tender spleen edge was now palpable about three fingerbreadths below the left costal margin and her scleras were noted to be icteric. The white blood count was 19,350; the hemoglobin was 7.5 gm. and red cell fragility studies showed increased resistance of the patient's cells to hemolysis. The icterus index was 42 with a strongly positive direct van den Bergh. Urine urobilinogen was positive in a dilution of 1:500. The serum total protein was 5.3 gm. per 100 cc. with an albumin-globulin ratio of 1.5. She was given a transfusion of 500 cc. of group "O," Rh positive blood. Penicillin, 40,000 units intramuscularly every three

hours, was given. (Fig. 1.) During the next three days the temperature fluctuated between 100°F. and 105°F., and she had two shaking chills. She complained of severe pains in her legs and pretibial bone tenderness was exquisite. Blood cultures, with a penicillin in-

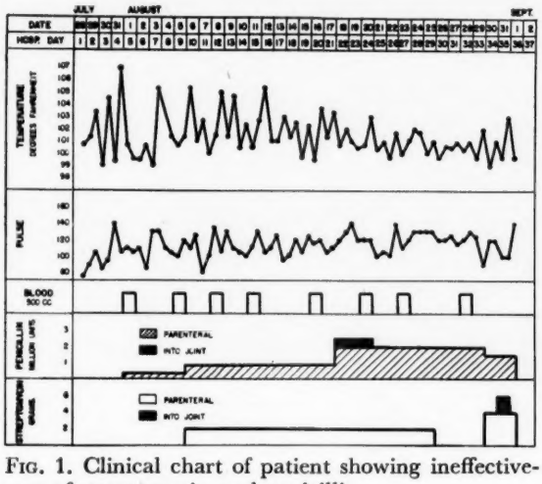

FIG. 1. Clinical chart of patient showing ineffectiveness of streptomycin and penicillin.

hibitor added, remained sterile but a urine culture was reported "95% growth of Bacillus capsulatus mucosus and 5% growth of Esch. coli."

On the morning of the eighth hospital day pains in the legs persisted and she complained of a painful right knee joint. The temperature remained elevated. Scleral icterus was minimal. Fine crepitant rales were still heard at the right lung base. The right knee joint was now swollen, hot and tender with signs of effusion. Attempts to aspirate this joint were unsuccessful. A bedside chest film showed residual pneumonitis at the base of the right lung. A film of the right knee joint showed narrowing of the joint space with slight spur formation. (Fig. 2.) X-rays of the skull and long bones were negative. Sternal marrow examination revealed slight increase of the myelocytes but was otherwise normal. The reticulocyte count remained 2 per cent.

On the tenth hospital day she experienced another shaking chill, continued to complain of pain in the right knee and now pain in the left knee joint developed as well. Both knee joints were hot, swollen and tender. Penicillin was increased to a dose of 100,000 units every three hours and streptomycin was given intramuscularly every three hours to a total of 2.0 gm. daily. Over the next week the patient continued to run a septic course with chills and fever in spite of chemotherapy. Both knees

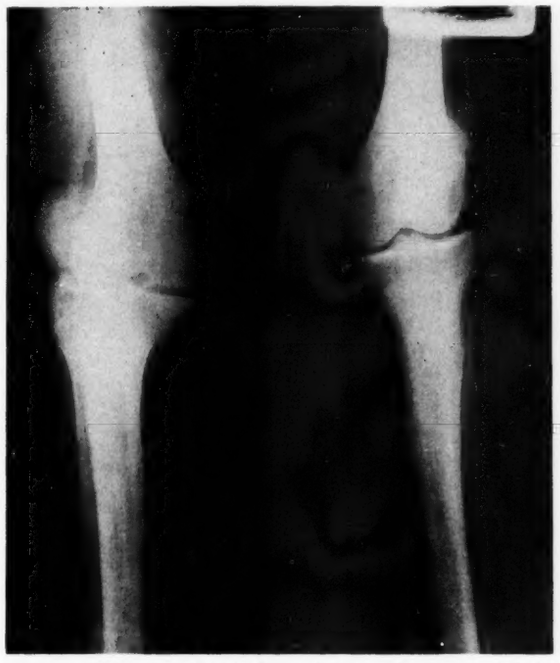

FIG. 2. X-rays of both knee joints taken on eighth hospital day. On the left, the right knee joint shows narrowing of the joint space with slight spur formation. On the right, the left knee joint appears normal.

remained painful, swollen and tender. The right leg showed pitting edema down to the ankle. Her hemoglobin level remained at 8.0 gm. in spite of three additional transfusions. Leukocytosis between 14,000 and 18,000 persisted as did albuminuria. Urine cultures became negative after streptomycin therapy. Agglutinations for enteric pathogens were all negative. The icterus index rose to 46. Cold agglutinins were present in a titer of 1:8.

Aspiration of the right knee joint on the nineteenth hospital day produced 20 cc. of thick, brownish, foul-smelling pus which on smear and culture revealed a non-hemolytic streptococcus and a hemolytic Esch. coli organism. Streptomycin sensitivity studies found the Esch. coli to be sensitive to "not less than 20 micrograms of streptomycin per cc. and resistant to 0.15 mg. of sulfadiazine per cc." This report was not received until three days before the patient's death. X-ray of this right knee joint, taken on the twenty-second hospital day (Fig. 3), revealed marked destruction of the joint space, beginning osteomyelitis of the adjacent bone and marked soft tissue swelling. Figure 4 shows the right leg with circumscribed areas of decreased density, interpreted as gas, in the calf and periarticular areas of the joint. Crepitation on palpation confirmed the presence of gas.

3 4 5

FIG. 3. X-ray of the right knee joint on the twenty-second hospital day showing marked destruction of the internal portion of the joint space with soft tissue swelling and beginning osteomyelitis.
FIG. 4. X-ray of the right leg on the twenty-second hospital day showing circumscribed areas of decreased density consistent with gas in the soft tissue.
FIG. 5. X-ray of the left knee joint on the thirty-third hospital day, showing narrowing and blurring of the joint space with periarticular areas of gas formation.

Surgical drainage of the right leg and right knee joint produced about 800 cc. of brown, foul-smelling pus which again revealed nonhemolytic streptococcus and hemolytic Esch. coli. Anaerobic cultures were negative for clostridial organisms as well as bacteroides.

During the next week the right leg drained copious amounts of purulent material. There was some subjective relief of pain in the right knee and leg, but the left knee became progressively more painful and swollen. Streptomycin was stopped after twenty days of therapy, totalling 40.0 gm.

On the thirty-second hospital day the left knee joint felt crepitant and x-ray confirmed the presence of periarticular gas. (Fig. 5.) Surgical incision of the left knee joint released 400 cc. of foul pus which also grew out the same two organisms. Streptomycin, 4.0 gm. per day, was reinstituted. Both legs continued to drain profusely. In spite of frequent irrigation of the draining wounds in both knee joints, the local instillation of streptomycin and frequent transfusions, the patient's course became steadily worse and she died on the thirty-fifth hospital day.

Postmortem examination was conducted sixteen hours after death. Both legs were swollen and had a foul odor. The skin over both calves was wrinkled, moist and peeled easily. There were several deep, longitudinal incisions draining pus. There was swelling of both knees. The tissues immediately beneath and around these incisions was entirely necrotic and purulent.

The peritoneal cavity contained no fluid. There were dense fibrous adhesions binding together the gallbladder, liver, duodenum and hepatic flexure of the colon. There were numerous fibrous adhesions from the spleen to the surrounding structures. The pleural cavities contained no fluid. The lungs together weighed 850 gm. There were fibrous adhesions between the right lower lobe of the lungs and the diaphragm. The lungs were crepitant throughout.

The heart weighed 270 gm. The epicardium, myocardium and endocardium were all normal. There was no sclerosis of the coronary arteries. No abnormality of the valves was noted.

The spleen weighed 470 gm. and the surface was rough. The liver weighed 1,760 gm. There was an abscess 3 cm. in diameter in the left lobe 1 cm. below the anterior surface near the inferior margin. No other abscesses were grossly visible. The gallbladder was small and its wall was thickened. There were two small pigment stones in the cystic duct. One of the stones almost eroded through the mucosa of the duodenum about 3 cm. above the ampulla of Vater

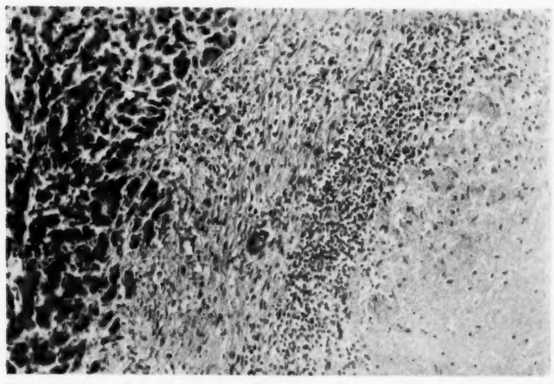

FIG. 6. Sections at periphery of liver abscess showing necrotic area, fibrous zone and normal liver tissue; × 350. (Army Inst. of Path. Neg. No. 205878-2.)

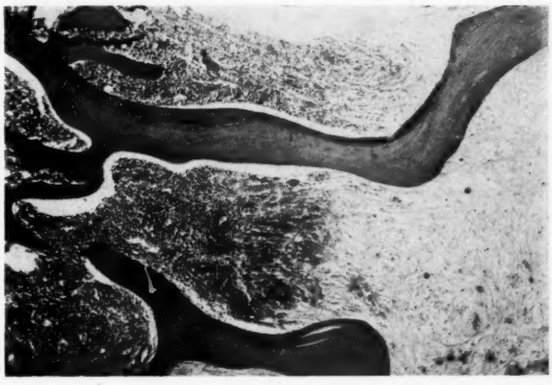

FIG. 7. Lesion in bone marrow showing zone of hemorrhage between hyperplastic marrow and area of sclerosis; × 80. (Army Inst. of Path. Neg. No. 205878-1A.)

and was clearly visible from the lumen of the duodenum. A patent cystic duct could not be demonstrated. The hepatic and common ducts were patent and bile stained. The left kidney weighed 260 gm. and the right 170 gm. Both kidneys were yellow-brown and flabby. The capsules stripped with great difficulty and revealed a uniformly granular surface. On section the usual markings were completely obliterated and it was impossible to measure the cortices. The pelves including the calices were greatly enlarged. The pancreas, adrenals, ureter, urinary bladder and genital organs were all normal to gross examination.

The bodies of the vertebral bones were yellow-brown and soft. In some areas there were irregular deep yellow zones 5 mm. in diameter surrounded by a ring of hemorrhage. The bones surrounding the knee joints were involved in the inflammatory process.

The cranial cavity and brain were not examined.

Postmortem culture of heart's blood grew out non-hemolytic streptococci and hemolytic Esch. coli. Cultures of the liver abscess and both kidneys grew out hemolytic Esch. coli.

Microscopic examination of the right lung showed several small areas of collapsed alveoli. Some of the alveoli of the right lower lobe were filled with edema fluid and very few neutrophils. The left lung was essentially normal.

Two sections of the liver revealed a moderate amount of brown pigment in the Kupffer cells. In one section there was a large necrotic area and just outside this area was a darker staining fibrous zone. (Fig. 6.) At the periphery there were numerous lymphocytes, monocytes and macrophages filled with brown pigment. There were other smaller areas of necrosis seen. An acid-fast stain showed no acid-fast organisms, although numerous bacilli were seen in the wall of the liver abscess.

The spleen was congested. The red pulp was full of large mononuclear cells, many of which were myeloblasts and a few eosinophils. Numerous normoblasts were seen. A few small multinucleated giant cells resembling megakaryocytes were present.

Sections of both kidneys revealed almost complete obliteration of the cortex with very few glomeruli visible. Those glomeruli seen were essentially normal. There was considerable scarring of the remaining cortex and of the medulla with a great increase in the interstitial connective tissue. The tubular epithelium of both the cortex and medulla was swollen and granular. There were several foci of necrosis. There was a generalized interstitial cellular infiltration of lymphocytes, plasma cells and monocytes. The pelvic subepithelial connective tissue was thickened and edematous and contained chronic inflammatory cells. These findings were consistent with severe chronic pyelonephritis.

Sections of the gallbladder revealed chronic cholecystitis.

Only sections from the right knee joint were examined microscopically. The right tibia and surrounding soft tissue near the knee joint revealed a chronic inflammatory reaction consisting of lymphocytes and monocytes. In the bone marrow there was a large, fairly well circumscribed area of hemorrhage. The bone marrow was hyperplastic, showing an excess of myeloid elements. Acid-fast stain revealed no organisms.

A section of lumbar vertebra showed almost

complete absence of normal structure. The central portion of the lesion which in the gross was a deep yellow was composed of dense collections of fibrin. The spicules were still present but most of the calcium had been resorbed. Surrounding this central zone there was a narrow zone of hemorrhage. Outside the zones of hemorrhage the bone was normal except for advanced hyperplasia of the myeloid elements and to a lesser extent of the erythroid elements of the marrow. (Fig. 7.)

The ribs and sternum revealed markedly hyperplastic marrow, predominantly of myeloid elements but including erythroid elements as well.

The pancreas, thyroid, adrenals, ovary and uterus were all normal.

COMMENTS

Although the major clinical problem in this patient was that of combatting an overwhelming bacterial infection caused by Esch. coli and non-hemolytic streptococci, several other salient features became apparent from the postmortem findings. A diagnosis of sickle cell anemia with secondary infection was considered clinically because of the positive sickling trait, the anemia, the icterus and the severe bone pain.[16] However, sternal marrow smears revealed no relative or absolute increase of the erythrogenic elements but rather an increase in the myeloid elements. Further, the skull x-rays and reticulocyte counts were not those of sickle cell anemia. At autopsy the hyperplastic blood elements were mainly those of the myeloid series. The infarcts in the bone marrow and the multiple thromboses, although compatible with sickle cell anemia, may well have been due to sepsis without sickle cell crisis. The finding of pigment stones in the gallbladder was consistent with chronic hemolytic episodes in the past, and it was thought that the patient had a sickling trait without the specific anemic crisis.

Another cause for the anemia was considered. The frequent blood transfusions were given with cold blood, but the patient's hematocrit showed very little response. However, since the patient's cold agglutinin titer was not high and transfusions with warm blood did not bring about any better response than originally, the possibility of hemolysis by cold agglutination was not further considered.

The failure to obtain a positive blood culture during life was unfortunate but chemotherapy could adequately explain the negative cultures. The postmortem culture of the same two organisms, nonhemolytic streptococcus and Esch. coli, from the heart's blood and the recovery of the Esch. coli from the liver abscess and the kidney pelves left little doubt that the patient had an overwhelming bacteremia during life with metastatic suppuration. Despite the fact that urine cultures were negative after streptomycin was given, the findings of so marked a chronic pyelonephritis seemed to point to the kidneys as the primary focus and the arthritis and liver abscess as secondary areas of infection.

Perhaps the most interesting aspect of the clinical picture was the production of gas in the periarticular tissues of the knee joints and in the subcutaneous areas of the right leg. Whereas the non-hemolytic streptococci do not generally form gas in their metabolism, sugar fermentation with the liberation of gas by Esch. coli is quite possible.[17] Since a thorough bacteriologic search was made for anaerobic gas-producing clostridial organisms and for bacteroides, there seems little doubt that the Esch. coli bacillus was responsible for the subcutaneous emphysema.

A final aspect deserving of consideration is the actual chemotherapy used and the relationship of streptomycin dosage to the drug sensitivity of the organism. The *in vitro* resistance of the Esch. coli isolated from the joint pus to 15 mg. per cent of sulfadiazine, combined with the patient's severe kidney disease, made streptomycin the antibiotic agent of choice (prior to discovery of aureomycin). Not only was one dealing with a bacteremia but also the additional problem was that of delivering the drug in adequate concentration to walled-off foci of infection in the synovial joint space and liver. There

was the further complication of a mixed infection by two organisms.

Whereas Keefer[13] and others[18,19] have reported encouraging results with streptomycin in the treatment of Esch. coli bacteremia, rational therapy makes it necessary to determine whether a sufficiently high blood concentration is being maintained with reference to the sensitivity of the bacteria isolated from the patient. The varying serum concentrations reported by different workers after injection of similar amounts of streptomycin make it apparent that absorption of the drug is different for each patient. Heilman et al.[20] reported blood serum concentrations of 3 micrograms per cc. after intramuscular injection of 0.1 gm. every three hours although serum levels up to 12 micrograms per cc. have been reported on similar dosage.[21] More generally, however, it seems that intramuscular administration of 1.0 gm. daily, given in divided dosage every three hours, maintains serum levels between 5 and 10 micrograms per cc.[22] Pulaski and Sprinz[23] reported a mean blood serum level of 16 micrograms per cc. if 0.4 gm. is given every four hours. Intravenous administration of streptomycin may produce serum levels as high as 60 micrograms per cc.[24] but there is a rapid fall of this level upon cessation of administration. With the 2 gm. of streptomycin administered daily to this patient it would be expected that her serum concentration of drug never exceeded 15 micrograms per cc. Since the sensitivity of the organism was greater than 20 micrograms per cc., it is apparent that this blood level of streptomycin was inadequate.

Buggs et al.,[25] studying the *in vitro* action of streptomycin on bacteria, isolated twenty-six strains of Esch. coli from twenty-one different patients and found that 73 per cent of these strains were sensitive to a concentration of 8 micrograms or less per cc. Pulaski[23] considers organisms inhibited by 16 micrograms of streptomycin per cc. as being sensitive if the focus of infection is dependent on drug delivered by the blood stream. A localized suppurative process in the joint space, as existed in this patient, raised the additional problem of delivering streptomycin in suitable concentrations from the blood stream to the actual focus. Florey[26] and others[27] have explained the failure of streptomycin to sterilize localized, walled-off cavities of infection as being due to the acidic nature of autolyzing tissue and pus. Such lowering of the hydrogen ion concentration may inactivate streptomycin which is slightly alkaline in reaction. *In vitro* studies show[26] streptomycin to be more effective at pH 7.0 than at pH 6.0. Thus earlier installation of streptomycin into the joint space may well have been beneficial to this patient.

A final explanation of streptomycin failure in this case was the possibility that streptomycin resistance may have developed during treatment. Since therapy was instituted prior to the isolation of the Esch. coli organism from the joint fluid, it was not known whether the sensitivity of the patient's strain of bacillus to over 20 micrograms per cc. represented initial streptomycin resistance or resistance which may have developed during treatment.[13,18,28] Knop[29] showed how most bacterial strains can be made resistant to extraordinarily high concentrations of streptomycin. Likewise, Murray et al.[30] demonstrated the development of streptomycin resistance by transfer of agar plate and broth cultures through increasingly higher concentrations of the drug, the resistance developing faster on agar plates than in broth. This difference between plate and broth resistance has practical implications in connection with the development of resistance by bacteria growing in pockets or walled-off spaces (as in this patient) in which the concentration of organisms is high and that of the antibiotic is low, or in some instances when the exposure of the organism to the antibiotic may resemble that of a surface growth. It appears essential, therefore, that bacteria be eradicated in the shortest possible time if satisfactory clinical results are to be attained. Under ideal conditions it seems best to use large doses of streptomycin from

the onset of treatment and to make frequent recourse to the laboratory for determination of sensitivity of the organism *in vitro* if the infection does not respond.

SUMMARY

A case of metastatic suppurative arthritis with subcutaneous emphysema caused by a mixed infection of Esch. coli and non-hemolytic streptococcus is presented.

The presence of marked anemia and a sickling trait in a Negro patient is discussed as a further complication in diagnosis.

The unsuccessful use of streptomycin in this patient is discussed in relation to the many factors which must be considered in using this drug.

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Canicola Fever with Meningitis*

Report of a Case in a Human Treated with Penicillin

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CANICOLA fever, an infection caused by Leptospira canicola, is primarily a disease of dogs. The spirochete was first distinguished from L. icterohaemorrhagiae in 1931 in Holland[1] and the first human cases were reported from that country in 1937.[2] Since then approximately 100 cases in man have been recognized in different parts of the world; six of them were in the United States. The last American case report was that of Rosenbaum[3] who also prepared an excellent review of the literature.

It is the purpose of this paper to describe a case encountered in Cincinnati in 1947 which is of particular interest because the patient was much more severely ill than most of those reported so far.

CASE REPORT

A thirty-two year old white man, a house insulator by occupation, was admitted to the Medical Service of the Cincinnati General Hospital on September 7, 1947, with the story that six days previously he had to quit work because of generalized muscular aching, malaise, anorexia and shaking chills. The latter were followed by a temperature of 104°F. A slight, dry cough appeared. Two days prior to admission he began to vomit blood-flecked, bile-stained material. He took a laxative which produced a watery diarrhea. The chills, daily remittent fever and vomiting continued until admission.

The patient owned four dogs. Two of them had recently died of "distemper" although the source of their illness was not known. The other two became ill with the same malady but recovered. The patient had been swimming in the Ohio River with one of the dogs two weeks prior to admission.

In 1939 he was admitted to the Cincinnati General Hospital because of hematemesis and melena. X-rays showed chronic duodenal ulcer. In 1945 he was treated for multiple staphylococcic abscesses of both legs. An x-ray of the chest one year prior to the present illness was reported as negative.

The patient was a well developed, well nourished, vigorous man appearing acutely ill but well oriented. He complained of nausea but no pain. His temperature was 102°F., pulse 100, respirations 26 and blood pressure 138/82. The skin was hot and dry but not icteric. The neck was not stiff. There was bilateral conjunctivitis with small bulbar hemorrhages but no petechiae. The nasal turbinates were injected. The lips were parched and the pharynx diffusely injected. There was generalized lymphadenopathy. The heart was normal and the lungs showed nothing remarkable except for a few rhonchi heard bilaterally over both lower lobes. The abdomen was scaphoid with normal peristaltic sounds; there was some resistance to palpation in both upper quadrants. The liver, which was very tender, was palpated three finger-breadths below the costal margin in the anterior axillary line. A questionable mass was felt in the left upper quadrant. There was slight left costovertebral angle tenderness. Neurologic examination was not remarkable.

Laboratory findings on admission included hemoglobin 10 gm. per cent, red blood cells 3,130,000 per cu. mm., white blood cells 12,350 with 78 per cent polymorphonuclear leukocytes, 12 per cent lymphocytes, 6 per cent eosinophils and 4 per cent monocytes. Since the patient was oliguric, no urine was examined at the time of admission. Blood culture was negative. Culture, guaiac test and microscopic examination of the stool were negative. The clotting time (capillary tube method) was six minutes. Blood urea nitrogen was 60 mg. per cent and the blood chlorides 436 mg. per cent. The Kahn

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reaction on the blood serum was negative. Roentgenogram of the chest on admission showed a normal heart and mediastinum; a small patch of infiltrate above the left diaphragm was interpreted as probable early pneumonia.

meningitis although no bacteria were found by smear or culture. Icterus now was visible in the sclerae. Throughout the third and fourth days the patient remained critically ill and on the fourth day he had two generalized convulsions.

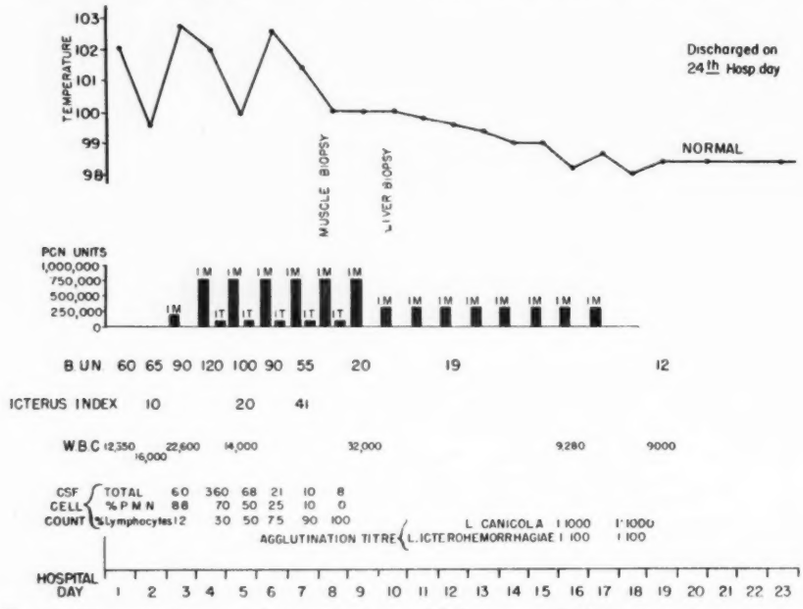

FIG. 1. Temperature graph, treatment and laboratory findings in a human case of canicola fever.

The admission diagnosis was virus-type pneumonia although one observer suggested the possibility of Weil's disease because of the combination of anuria and hemorrhagic phenomena. The temperature, important laboratory studies* and penicillin treatment are presented in Figure 1.

Although no chemotherapy was given at first, the patient's temperature fell to 98.8°F. on the second hospital day. However, he vomited all that day. By evening he was worse and vomited fresh blood. The appearance in a severe, acute, febrile illness of oliguria, conjunctival hemorrhages and gastric bleeding suggested the possibility of Weil's disease and, with this as a working diagnosis, the patient was given 30,000 units of penicillin every three hours beginning at midnight of the second hospital day. This was soon increased to 100,000 units every three hours. The next morning (third hospital day) the patient's temperature rose to 102.8°F. The patient was delirious and had three generalized convulsions. The spinal fluid gave evidence of

* The leptospira agglutination tests were performed by the Division of Tropical Diseases, National Institutes of Health, Bethesda, Md., through the courtesy of Drs. F. J. Brady, John E. Tobie and John Bozecevich.

He passed no urine. On the fifth hospital day (the third day of penicillin therapy) he was remarkably improved and passed 1,400 cc. of dark amber urine of low specific gravity. From then on improvement was steady. On the sixth day the patient's temperature again reached 102°F. but it fell nearly to normal the same day. Intramuscular penicillin therapy was continued until the eighteenth hospital day and in addition 10,000 units in 10 cc. saline were given intrathecally during the fourth through the eighth days. He was discharged on the twenty-seventh day.

Laboratory tests performed during the patient's course but not shown in Figure 1 were as shown in the table on page 251.

Biopsy* of the deltoid muscle on the tenth hospital day revealed the following: Grossly, the specimen consisted of an irregular greyish pink piece of tissue measuring 2.5 by 0.5 by 0.2 cm. Microscopically, the section showed focal degenerative lesions in skeletal muscle which consisted of sharply localized areas of basophilic hyalinization, vacuolization and sarcolemmal proliferation. Neither inflammatory reaction

* This biopsy was interpreted by Dr. Edward A. Gall, to whom we are greatly indebted.

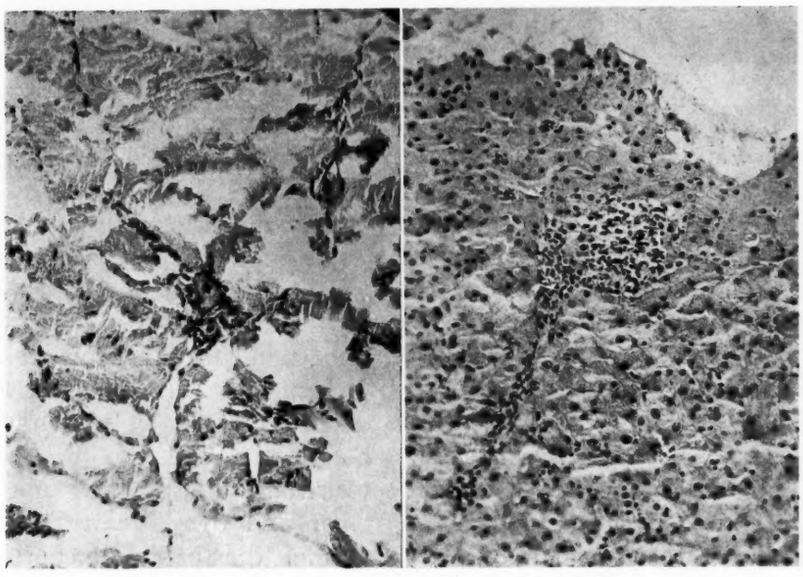

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FIG. 2. Muscle biopsy from a case of canicola fever. Despite artifactual distortion one may identify two swollen muscle cells with darker staining than the adjacent normal elements. Characteristic are the large hyperchromatic nuclei and pronounced sarcolemmal proliferation. Inflammatory cells are inapparent.
FIG. 3. Liver biopsy from a case of canicola fever. Normal appearance and relations persist. A large collection of lymphocytes is present which indicates the site of focal liver cell necrosis.

Liver Function Tests	2nd day	6th day	21st day
Thymol turbidity	2 units	3 units	7 units
Thymol flocculation	negative	2+	1+
Cephalin-cholesterol flocculation	negative	negative	negative
Alkaline phosphatase	3.3 Bodansky units		
Serum bilirubin (prompt)	0.8 mg.%	2.1 mg.%	0.4 mg.%
(total)	2.3 mg.%	2.3 mg.%	1.0 mg.%

Serum Protein:	
7th hospital day	5.9 gm. %
24th hospital day	7.9 gm. %
Serum Agglutinations:	1st day
Typhoid, O and H	negative
Paratyphoid, A and B	negative
Brucella	negative
Sheep red blood cells	negative

CEREBROSPINAL FLUID (FIG. 1):

Hospital Day	Initial Pressure	Final Pressure	Gross Appearance	White Blood Cells	Protein	Sugar	Chloride
3*	330	170	slightly pink	400	50 mg.%	88 mg.%	637
4	260	130	xanthochromic	230	.....	.....	...
5	220	130	xanthochromic	810	.....	.....	...
6	200	130	clear	18	.....	.....	...
7	110	70	clear	10	.....	.....	...
13	80	50	clear	0	.....	.....	...

* Wassermann, gold curve, smear and culture negative

nor hemorrhage was apparent. (Fig. 2.) These lesions were unique in the examiner's personal experience and resembled those described by Sheldon in Weil's disease. The diagnosis was focal muscle degeneration consistent with Weil's disease.

Liver biopsy* on the twelfth hospital day revealed the following: The parenchyma was well preserved. There were neither intracellular nor intralobular lesions of note. Very occasional small collections of lymphocytes and polymorphonuclear leukocytes were evident in lobules with evidence of tissue destruction. (Fig. 3.) The diagnosis was focal hepatitis, slight (Weil's disease).

COMMENTS

Of approximately 100 cases of canicola fever so far reported nearly half have occurred in Holland.[4] Six cases have been described in the United States.[3] The disease is clinically indistinguishable from Weil's disease due to L. icterohaemorrhagiae although the mortality in canicola fever is much lower. To date only one death from canicola fever has been reported.[5]

The incubation period is probably the same as in Weil's disease, namely, one to two weeks. The onset is usually sudden and

*This biopsy was interpreted by Dr. Edward A. Gall, to whom we are greatly indebted.

is characterized by myalgia, chills, high fever and conjunctivitis. The disease may be mild. Jaundice, far from being constant, is present in a minority of patients. Involvement of the kidney is more common. Oliguria and elevation of the blood urea nitrogen to more than 100 mg. per cent are not rare. One of the most constant features of the reported cases is meningitis. For example, involvement of the cerebrospinal fluid was encountered in sixteen of seventeen cases reported by Minkenhof[4] from the Wilhelmina Hospital in Amsterdam. It was seen in all four cases reported by Laurent et al.[6] from London. In fact, meningitis may be the only clinical evidence of the infection. Since the disease occurs in the summer and early fall, it has sometimes been confused with the various virus meningitides and with preparalytic poliomyelitis. The illness usually lasts two to five weeks and convalescence is long.

Polymorphonuclear leukocytosis is the rule and is sometimes helpful in differentiating the disease from infectious hepatitis. The causative organism may be isolated from the patient's urine during the second week of the illness[3,7] and occasionally from the spinal fluid when meningitis is present. The most important test in the diagnosis of canicola fever is the agglutination-lysis test of Schuffner and Mochtar[8] or one of its modifications.[9]

The case reported herein is one of the most severe on record. The patient exhibited nearly every sign and symptom so far reported in human cases of canicola fever,[3] namely, chills, fever, muscle pains, conjunctivitis, ecchymoses, jaundice, anuria and meningitis.

The muscle and liver biopsies are of special interest because the pathologic changes in human beings have not been previously described. The liver biopsy (Fig. 2) showed focal hepatitis compatible with but not diagnostic of Weil's disease. To our knowledge this is the only case of canicola fever in which a muscle biopsy showed the lesions described by Sheldon[10] as pathognomonic of Weil's disease. This would indicate that the lesions seen by Sheldon occur in other leptospiral diseases.

Patterson[11] reported a small series of cases of Weil's disease which were favorably affected by penicillin therapy. Heilman and Herrell[12] have reported the successful treatment of experimental Weil's disease with penicillin. Accordingly, our patient was given penicillin intramuscularly and intrathecally. Within twenty-four hours after penicillin therapy was instituted the patient was clinically markedly improved, and within forty-eight hours his temperature began to fall. From the eighth to the fifteenth hospital day he ran a very low grade fever and thereafter remained afebrile. It was felt that penicillin shortened the febrile period and may have saved the patient's life. This might have been expected from the reports by Alston and Broom[13] who showed that penicillin had lethal and inhibiting effects *in vitro* on L. canicola. Our experience is in keeping with that of Baber and Stuart[14] in England who successfully treated a case of human canicola fever with penicillin in 1946.

In some of the patients, as in our case, there has been a history of association with dogs and sometimes sick dogs. Swimming in rivers had also preceded the onset of the disease in a number of cases.[15] Leptospirosis canicola is apparently a very common disease in dogs as judged by the incidence of antibodies to L. canicola in the dog population of various parts of the world.[16,17] It has been reported to vary between 4 and 38 per cent. Since the disease is believed to be transmitted through contact with dog's urine, one wonders whether human infection with L. canicola may not be more prevalent than present statistics indicate.

SUMMARY

A case of severe canicola fever, apparently contracted from a sick dog, is described. The chief clinical features were those of Weil's disease, namely, chills, fever, headache, muscle pains, delirium, ecchymoses, jaundice, anuria and meningitis. Striking

improvement was manifest within twenty-four hours of the administration of penicillin.

Muscle biopsy revealed lesions previously described in Weil's disease. Liver biopsy showed focal hepatitis although liver function tests were within normal limits.

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Paroxysmal Ventricular Tachycardia of Prolonged Duration*

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PAROXYSMAL ventricular tachycardia which fails to respond quickly to quinidine or other drugs and persists for weeks or months is a serious medical problem and challenge. Isolated instances of unusually prolonged ventricular tachycardia have been recorded.[1–8] In the one being reported normal sinus rhythm was restored after fifty-seven days during which both the older and the newer drugs recommended for this arrhythmia were employed.

W. S., No. 578927, a physician aged sixty, first came under the observation of one of us (H. L.) in March, 1947. For many years he was aware of sensitivity to milk and milk products manifested by attacks of right upper quadrant pain simulating cholecystitis. Several studies of the gallbladder with the use of dye showed no abnormality in this viscus. On stopping the ingestion of milk these abdominal symptoms remitted. The craving for milk would at times overcome him and indulgence in milk would be followed by fits of sneezing.

In 1937 following incision of an infected finger glycosuria and blood sugar of 200 mg. per cent were discovered. The subcutaneous injection of a small dose of insulin induced severe urticaria. Attempts at desensitization to insulin proved unsuccessful as the most minute dose of insulin in very high dilution provoked urticaria and, in addition, on two occasions auricular fibrillation diagnosed clinically in the first episode and confirmed by the electrocardiogram in the second. With diet alone the blood sugar was reduced to 145 mg. per cent and insulin was never taken thereafter.

The patient was fond of walking, had always enjoyed an energetic and active life and had had no symptoms of cardiovascular disease with the exception of the two episodes of irregularity already noted. Routine electrocardiogram in October, 1946, was normal, showing sinus rhythm, left axis deviation and a ventricular rate of 70 beats per minute. The T waves were upright in leads I and II, inverted in lead III and upright in lead IV F. Small Q waves were present in leads I and III; the PR interval measured 0.20 second.

The first evidence of heart disease occurred one night in March, 1947, when the patient suffered a mild attack of anterior chest pain. In the morning he felt well enough to go to his office but on returning from lunch the pressure in his chest recurred. An electrocardiogram taken that afternoon was reported as normal. Later in the evening the chest pain reappeared, radiated into the left arm and persisted for several hours. On the following morning (March 13, 1947) he was admitted to the Mount Sinai Hospital. His temperature on admission was 100.2°F. and the blood pressure was 176/128. The heart sounds were of fair quality with gallop rhythm heard best at the apex. There was no evidence of pulmonary congestion. The white blood cells numbered 13,500 per cu. mm. and the sedimentation rate (Westergren method) was 50 mm. per hour. The blood sugar was 200 mg. per cent and the CO_2 combining power 48.8 volumes per cent. Glycosuria of 1 plus and acetonuria of 4 plus were treated with intravenous sodium lactate solution in view of the striking sensitivity to insulin. The urine was acetone-free subsequently.

An electrocardiogram taken on the first hospital day (Fig. 1A) showed regular sinus rhythm, left axis deviation, an inverted T wave in lead I, a flat T wave in lead II and a prominent Q3. In the precordial leads CF2, CF4 and CF5 deeply inverted T waves without concomitant Q waves were present; these electrocardiographic changes suggested acute coronary insufficiency. Dicumarol® therapy, started immediately after admission, was stopped tempo-

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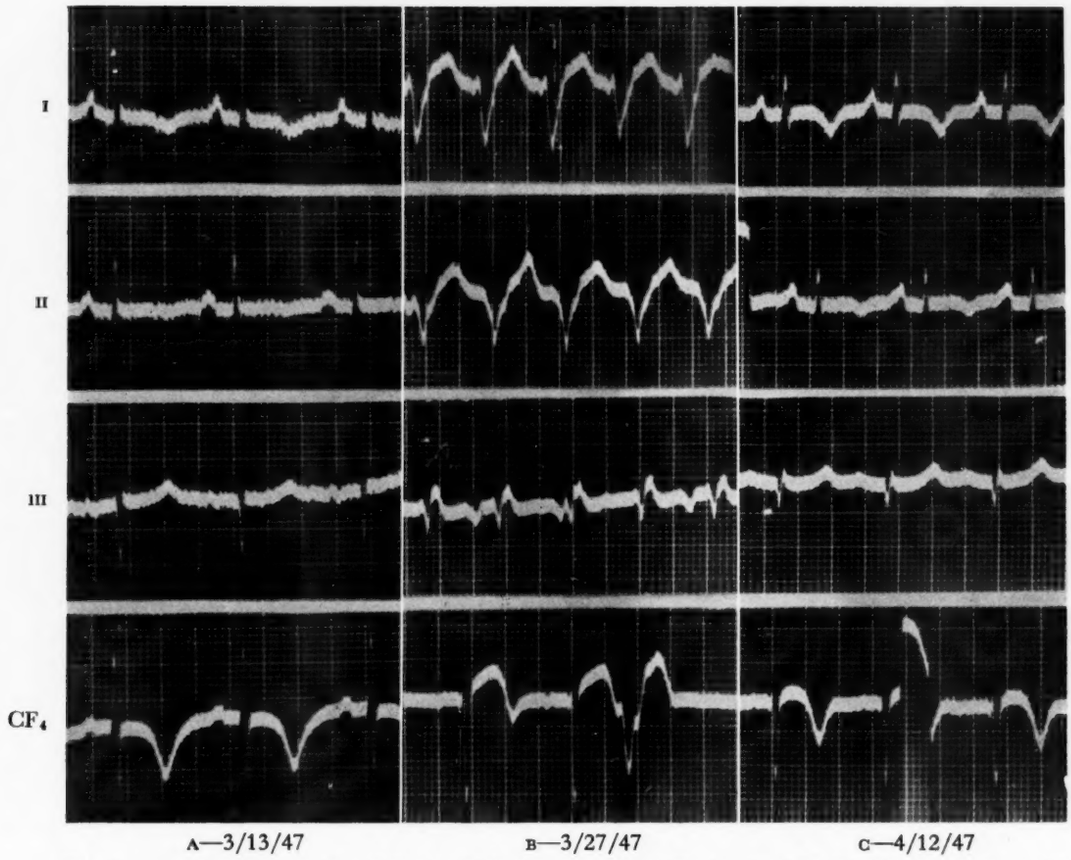

FIG. 1. A, regular sinus rhythm, left axis deviation, prominent Q_3, inverted TI, flat TII, deeply inverted T in CF_4; acute coronary insufficiency in premonitory phase of acute coronary occlusion. B, onset of acute anterior wall infarction with ventricular tachycardia at rate of 150; in lead CF_4 trigeminal rhythm produced by two sinus beats followed by a ventricular premature contraction; deep Q, elevated RS-T and diphasic T in CF_4. C, return to regular sinus rhythm; TI, II and CF_4 inverted and coveplane. These represent progressive changes of recent anterior wall infarction.

rarily on the seventh day when the prothrombin time was unduly prolonged, possibly in some measure due to the use of salicylates for traumatic arthritis of the wrist following an intravenous infusion into a small wrist vein. The prothrombin time returned to normal in forty-eight hours and dicumarol® was restarted. A few days after admission the recurrence of chest pain in the form of repeated attacks of substernal oppression at rest and unrelieved by nitroglycerine suggested further coronary involvement. Finally on the thirteenth day (March 26, 1947) the patient suffered severe prolonged precordial pain with vomiting. The blood pressure dropped to 88 systolic; the diastolic pressure was immeasurable. The skin was cold and clammy and the pulse weak and thready at a rate of 120 beats per minute. The heart sounds became distant and a friction rub was audible. Gallop rhythm was also noted at this time. The electrocardiogram taken on the following day (Fig. 1B) exhibited in the standard leads, I, II and III and in CF1 ventricular tachycardia with a ventricular rate of 150. Leads CF2 and CF3 showed bigeminal rhythm due to the presence of a sinus beat closely followed by a ventricular premature contraction. In CF4 the rhythm became trigeminal, two sinus beats followed by a ventricular premature contraction. In CF5 the trigeminal rhythm was superseded by regular sinus rhythm. Inspection of the sinus beats in the precordial leads disclosed a deep Q wave in leads CF2, CF3, and CF4 and a small R wave in CF5. The ST segment was elevated in leads CF2, CF3, CF4 and CF5, and the T wave was diphasic in CF4 and CF5. In addition to the ventricular tachycardia the electrocardiographic findings were now classically those of an acute coronary artery occlusion with anterior wall infarction. Following this attack of chest pain slight fever was evident for a few days. The blood pressure rose to 114/80 and the sedimentation rate

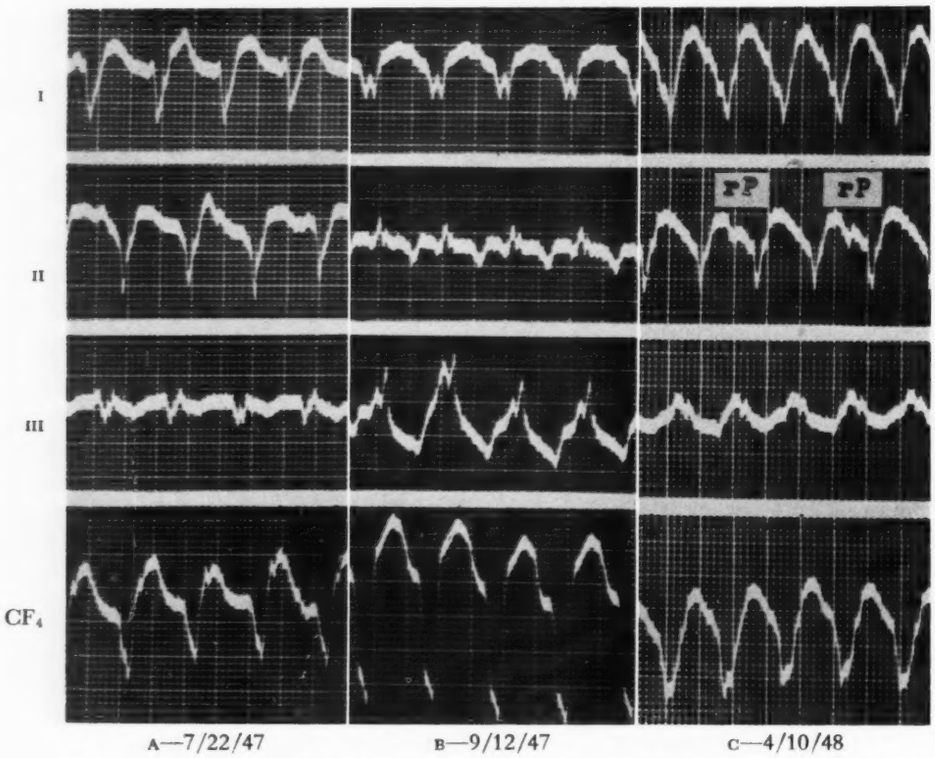

FIG. 2. A and B, two episodes of paroxysmal tachycardia from different ventricular foci. C, ventricular tachycardia during last admission; note alternately blocked retrograde (inverted) P waves (= rP) in Lead II.

finally dropped to 28 mm. per hour (Westergren method). An electrocardiogram repeated on April 12, 1947 (Fig. 1C), showed regular sinus rhythm; the premature contractions were no longer present. The T waves in leads I, II and IV were inverted and cove-plane; these findings indicated progressive changes of an anterior wall infarction. Dicumarol® therapy had been stopped on April 9, 1947. The remainder of the patient's hospital course was fairly smooth and he was discharged on April 28, 1947.

At his home mild activity appeared to precipitate some degree of cardiac failure and this was controlled by digitalis and occasional injections of a mercurial diuretic. On June 20, 1947, he was awakened in the night by marked orthopnea, dyspnea and the expectoration of bloody, frothy sputum. This was relieved by morphine. Mercuhydrin given at intervals of three to five days induced excellent diuresis and there was no recurrence of orthopnea. On examination at the office on June 27, 1947, the blood pressure was 140/90. The lungs were clear; the heart sounds were dull. Fluoroscopy revealed marked enlargement of the left ventricle and a moderate degree of enlargement of the left auricle. The electrocardiogram showed some recovery toward normal of the T wave in lead I; the T wave in lead II was flat. In the precordial leads a prominent Q wave and elevation of the ST segment were still present. The urine showed a specific gravity of 1.020; there was no albuminuria but slight glycosuria was present. The patient was re-examined on July 22nd when he stated that for four days he had had rapid heart action without subjective discomfort. There was no dyspnea or evidence of pulmonary congestion. The blood pressure was 120/90. The heart sounds were dull; the rate was rapid. The electrocardiogram showed the presence of ventricular tachycardia at a rate of 150. (Fig. 2A.) He was given oral quinidine sulfate (6 gr. every two hours for six doses on each of three successive days) without altering the mechanism. When the tachycardia had been present for six days, quinidine sulfate was again administered (6 gr. at two-hour intervals for five doses); immediately thereafter 5 gr. of quinine dihydrochloride were injected intramuscularly in the course of two minutes. About one-half minute after the completion of the injection regular rhythm was suddenly restored; the rate was 80. This per-

sisted for five hours when the rate again rose to 150. This lasted for twenty-five minutes and then broke once again to 80. The next day the rate was still 80 beats per minute. The patient had diarrhea, tinnitus and felt quite weak. The tachycardia recurred the next day; and since it was not controlled by 6 gr. of quinidine given every two hours for eight doses, the patient was again hospitalized at Mount Sinai Hospital on July 28, 1947. The electr ardiogram confirmed the presence of ventricular tachycardia. The patient was given 15 gr. of quinidine sulfate by mouth at 4 P.M., 6 gr. at 5 P.M. and 6 gr. at 7 P.M. At 8:30 P.M. 7 gr. of quinidine hydrochloride (Brewer) were given intramuscularly. At 10 P.M. 6 gr. of oral quinidine were administered and again at 11 P.M. 7 gr. of quinidine hydrochloride were injected intramuscularly. The tachycardia broke sometime during the night for on the following morning regular rhythm at the rate of 80 was discovered and the patient was quite comfortable. The quinidine dosage was then reduced to 6 gr. every four hours and he was discharged on July 31, 1947. During the next two months he returned to his usual medical duties and felt fairly well. He walked freely and did not tire readily. On October 30, 1947, ventricular tachycardia recurred, provoked by some excitement at his office. He remarked that he had been eating a fair amount of cheese for three days prior to this attack. In view of his history of allergy to milk and milk products this took on some significance. During the summer months of 1947 he had noted short periods of tachycardia (Fig. 2A and B); some of these followed indulgence in milk. This latest attack of ventricular tachycardia was abolished after taking 6 gr. of quinidine orally every hour for several doses until tinnitus, nausea and marked apathy appeared. Ventricular tachycardia recurred on March 26, 1948, and after it had persisted for ten days he suffered an attack of acute pulmonary edema for which digitoxin, 0.8 mg., was given intravenously followed by maintenance doses of digitalis.

He was admitted to the Mount Sinai Hospital on April 6, 1948, for the third time. The heart rate was rapid; pulsus alternans was present; the blood pressure was 124/88. The lungs were clear on auscultation and there was no peripheral edema. In view of signs of quinidine toxicity and the absence of cardiac failure both the quinidine and digitalis were discontinued on admission to the hospital. The electrocardiogram (Fig. 2C) showed ventricular tachycardia with retrograde P waves. A clinical trial of potassium chloride was then suggested. This drug was given in doses of 15 gr. three times daily for the next two days but no basic change was noted either in the rhythm or the rate. For the next six days quinidine sulfate, 6 gr. every two hours, and potassium chloride, 15 gr. three times daily, were continued simultaneously. Nausea and vomiting reappeared and both drugs were discontinued on April 13, 1948. Immediately thereafter quinidine sulfate in dosage of 6 gr. every four hours was started and continued for five days. Again there was no change in the rhythm as checked repeatedly by electrocardiograms. On April 20th quinidine sulfate in dosage of 6 gr. every hour was given for ten hours. Repeated electrocardiograms were still unchanged. On this day some basal pulmonary congestion was noted and it was relieved quickly with mercurial diuretics.

In another therapeutic attempt procaine hydrochloride was given intravenously on the basis of the studies of Burstein and associates.[9] On April 21, 1948, the patient showed no reaction to procaine on intradermal test using 0.5 cc. of a 2 per cent solution. Accordingly 325 cc. of a 0.1 per cent solution of procaine hydrochloride containing a total of 325 mg. of the drug were given intravenously in the course of twenty-three minutes. Continuous electrocardiographic tracings were recorded throughout this experiment. There was not the slightest change in rhythm. Shortly after this intravenous injection carotid sinus pressure was applied and this also was without effect. The procaine appeared to induce a general feeling of relaxation but there were no other subjective symptoms. Electrocardiographic record taken the following day showed retrograde P waves after every QRS and this record appeared to be somewhat similar to a 2:1 auricular flutter. Because of the possibility of flutter the patient was again digitalized using digitaline nativelle, 1.2 mg. given in divided doses of 0.4 mg. and then maintenance doses of 0.2 mg. twice daily for the next four days. There was no change in the rhythm.

On April 26, 1948, intravenous procaine was tried for the second time; 700 cc. of an 0.1 per cent solution of procaine hydrochloride were injected intravenously within a period of twenty-four minutes. During its administration slurring of speech and diaphoresis were noted. The blood pressure remained steady at 120/100 and

the abnormal rhythm was unaffected. On April 29th 10 gr. of quinine dihydrochloride were given by intravenous drip in the course of sixteen minutes. This failed to influence the tachycardia. On the following day a similar dose was given intravenously within eight and a half minutes. For the first time some electrocardiographic changes appeared, the retrograde Wenckebach effect disappeared temporarily and the ventricular rate slowed slightly. In an attempt to prolong the "quinidine" effect 15 gr. of quinidine sulfate were administered orally; the retrograde P waves reappeared in the tracings taken shortly afterward. On the next day 10 gr. of quinine dihydrochloride, injected intravenously within four minutes, failed to alter the abnormal rhythm. On May 5th, the fourtieth day of continuous tachycardia, 10 cc. of a 10 per cent solution of magnesium sulfate were administered intravenously. This had no effect upon the tachycardia, producing only a generalized sensation of heat. On the following day 10 cc. of a 25 per cent solution of magnesium sulfate were given by the intravenous route and a definite change in the rhythm was noted for the first time. (Fig. 6A.) Bigeminal rhythm with alternation in the direction of the QRS complexes occurred and lasted for five hours. This was interrupted by short periods of trigeminal rhythm (two beats from the original focus with one from the second focus and vice versa) and was followed by gradual return to the original pattern of ventricular tachycardia. On May 7th a 20 cc. dose of 25 per cent magnesium sulfate was injected intravenously but the tachycardia was again unaffected. On this evening 8½ gm. of diethylaminoethanol hydrochloride[10] as an 11.2 per cent solution (Winthrop) were given by intravenous drip.* Aside from a slight drop in the blood pressure no change was noted.

Embolization to the right foot occurred on May 9th and was treated effectively by intravenous papaverine and repeated right lumbar sympathetic blocks with procaine. On May 10th on the basis of the possibility that we might be dealing with nodal tachycardia plus bundle branch block the use of strophanthidin acetate was suggested.† As the first dose 1 mg. was injected intravenously and then ¼ mg. every ten minutes until a total of 3.25 mg. had been administered. During this same period carotid sinus pressure was applied to heighten the vagus tone. Figure 6B shows the effect of the drug at the six and a half minute period. On this same day 25 mg. of mecholyl hydrochloride were injected subcutaneously; the basic abnormal rhythm was unaffected.

On May 11th propylthiouracil was started and continued for nine days in doses ranging from 100 to 300 mg. daily. It was hoped that depression of thyroid activity might favorably influence the action of other drugs upon the myocardium. By May 18th the patient had deteriorated noticeably. He suffered several bouts of paroxysmal dyspnea for which digitalis was readministered. On May 20th atabrine dihydrochloride, 0.4 gm., was injected intramuscularly, with no apparent change in the rhythm. On May 21st, the fifty-seventh day of continuous ventricular tachycardia, the patient was *in extremis;* the heart sounds were inaudible. The cardiac rate determined from the electrocardiographic tracings was 200 beats per minute. The blood pressure was 86 systolic and there was evidence of pulmonary congestion. Sometime in the mid-afternoon the patient experienced a severe bout of vomiting and shortly thereafter the pulse was found to be regular and slow. The electrocardiogram now showed regular sinus rhythm, rate of 98 beats per minute and evidence of an old anterior wall infarction (Fig. 6C). With the return of regular sinus rhythm there was dramatic clearing of the pulmonary congestion within a few hours and the patient, only recently moribund, was in relatively good health within a day. Oral atabrine in doses of 0.2 gm. twice daily was continued for several days. On June 1st the patient left the hospital. At this time the basic rhythm was regular with an occasional premature contraction.

On June 3rd while the patient was at his home resting quietly ventricular tachycardia recurred; there was no associated subjective discomfort. The cardiac rate was 160 to 180 beats per minute. The blood pressure was 110/70. The lungs were clear. On this day atabrine dihydrochloride in a single dose of 0.4 gm. was given intramuscularly. It produced no change and the following day a similar dose was given which produced slight cough, nausea and headache but no alteration in the tachycardia. On June 6th morphine sulfate, ¼ gr., and atropine, 1/150, were given intravenously and repeated seven hours later. An exquisite relaxation but no change in the tachycardia followed the administration of these

* This drug was given through the courtesy of Dr. J. Murray Steele.

† This rapidly excreted strophanthin derivative was furnished through the courtesy of Dr. Harry Gold.[11]

drugs. By June 21st the latest paroxysm of ventricular tachycardia had lasted eighteen days. In view of the fact that previously quinine dihydrochloride given intravenously in dosages of 10 gr. in the course of four minutes proved ineffectual, it was decided to increase the dosage terial. With the restoration of cardiac action regular sinus rhythm returned, broken only by an occasional extrasystole. The cardiac rate was 100 beats per minute. The intense nausea and retching persisted for over an hour. Three hours after the injection his color was fair and the

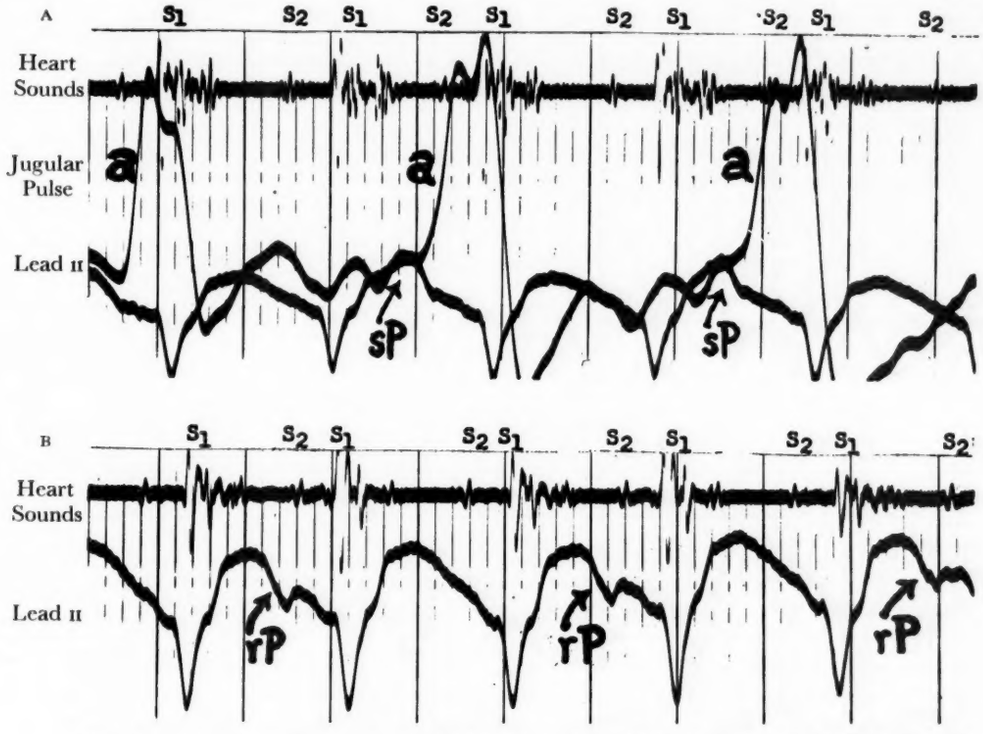

FIG. 3. A, simultaneous heart sounds, jugular pulse and Lead II; note high "a" wave of jugular pulse corresponding to preceding sinus P (= sP) wave and absent "a" wave following blocked P wave. B, simultaneous heart sounds and Lead II (overstandardized); rP = retrograde P wave; S_1 = first heart sound; and S_2 = second sound. Note early S_1 of high amplitude following rP compared with late S_1 of lower amplitude following blocked P wave.

of quinine to a point necessary for therapeutic effect as the situation by this time had become quite desperate; so on this day 22 gr. of quinine dihydrochloride were given intravenously in the course of two and a half minutes. The patient noted tinnitus after 4 gr. of the drug had been given. By the time the 22 gr. were introduced clonic twitching of the fingers and pectoral muscles were noticed. There was intense nausea and the patient felt that he was dying. Greenish pallor and much sweating were apparent. At this juncture, when no heart sounds had been audible for about forty seconds, 1 cc. of adrenalin, 1:1000, was injected intravenously. Within twenty seconds there was restoration of the heart beat. The pupils were partially dilated. Then intense nausea and severe retching set in and the patient salivated thick, tenacious ma-

rhythm was still regular with occasional dropped beats. The blood pressure was 110/82 and the cardiac rate was 96 beats per minute. The lungs were clear. Some nausea and general discomfort persisted throughout the night.

Regular rhythm persisted only until June 30th when ventricular tachycardia reappeared. That evening 32 gr. of quinidine sulfate were taken and during the night the rhythm returned to normal. However, after about eighteen hours ventricular tachycardia recurred. Despite this the patient felt fairly comfortable and insisted upon driving his car and even walking as many as twelve blocks at a slow pace. He did note some dyspnea on walking upgrade. On July 4th physical examination disclosed tachycardia at a rate of 180 and blood pressure of 110/70. The lungs were clear and there was no peripheral

edema. The succeeding two weeks were characterized by cardiac decompensation, marked depression over the course of his illness and refusal to take quinidine and mercurial diuretics. Finally on July 19th he took his automobile out of the garage, drove it a short distance from home and terminated his life with a gunshot wound to the right temple.

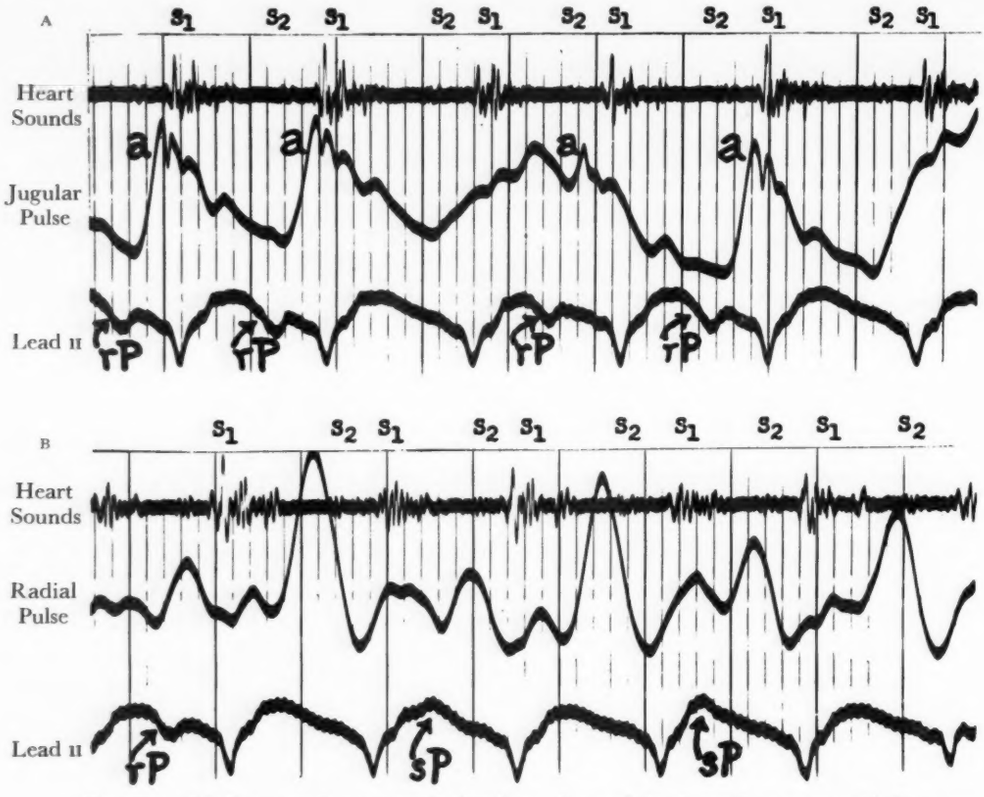

FIG. 4. A, simultaneous heart sounds, jugular pulse and Lead II; rP = retrograde P wave; S_1 = first heart sound and S_2 = second sound. Note high "a" wave of jugular pulse related to preceding retrograde P wave and absent "a" wave following blocked P wave with corresponding alternation of the heart sounds. B, simultaneous heart sounds, radial pulse and Lead II; rP = retrograde P and sP = sinus P waves. Note marked pulsus alternans unrelated to auricular activity and auscultatory alternans definitely related to preceding P waves.

Electrocardiogram taken on April 10th showed ventricular tachycardia, rate 175 beats per minute. (Fig. 2C.) It is noted in lead II that there are inverted P waves superimposed on the downstroke of alternate T waves. This on further study appeared to be ventricular tachycardia with retrograde auricular stimulation plus alternate retrograde A-V block. In further electrocardiographic studies on the same day there were sinus P waves and in some strips there were retrograde P waves superimposed upon the T waves of the preceding ventricular systole together with varying retrograde Wenckebach effect. Figure 3A shows studies done on April 10, 1948, in which heart sounds, jugular pulse and lead II of the electrocardiogram were taken simultaneously. In this record one notes the high "a" wave of the jugular pulse corresponding to a preceding sinus P wave. The "a" wave is absent when there is no auricular activity. In figure 3B heart sounds and lead II of the electrocardiogram (over-standardized) were taken simultaneously. Here the retrograde P waves are again seen on the downstroke of the T wave of the preceding QRS complex. It is noted that auricular contraction resulting from this retrograde P wave influences the succeeding systole in making the S1 (first heart sound) appear early and of high amplitude; whereas when the preceding retrograde P wave is blocked, the S1 is late and of low amplitude.

In order to study the effect on the jugular pulse of auricular systoles resulting from retrograde P waves, further studies were done on

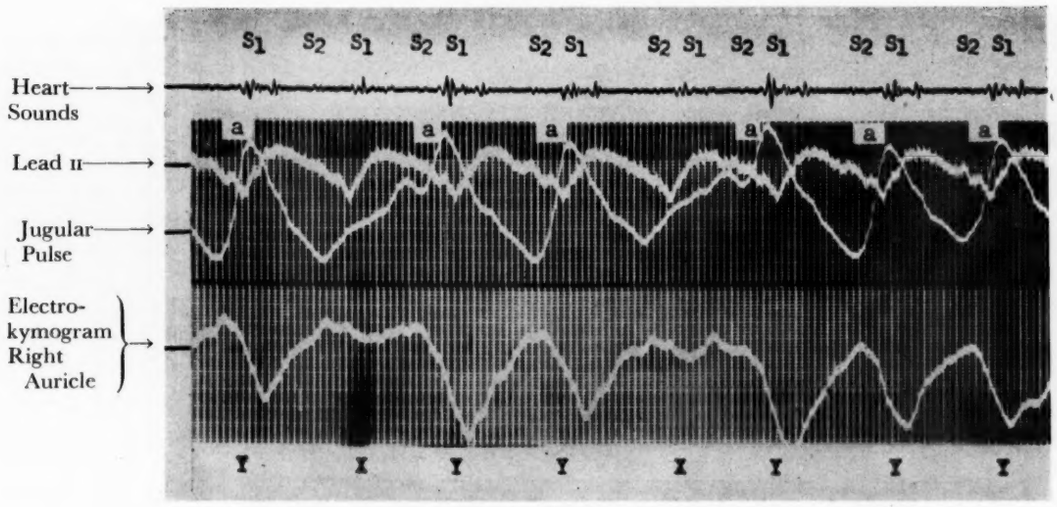

FIG. 5. Simultaneous heart sounds, Lead II, jugular pulse and electrokymogram taken over right auricle; S_1 = first heart sound; S_2 = second sound. "Y" = beats with: (1) early, accentuated S_1; (2) preceding P wave; (3) high "a" wave of jugular pulse and (4) presystolic downward deflection of electrokymogram beam indicating right auricular systole. "X" = beats with: (1) late, low S_1; (2) absent preceding P wave; (3) absent "a" wave of jugular pulse and (4) absent downward deflection of electrokymogram beam indicating absent right auricular systole.

April 22, 1948; a record (Fig. 4A) was taken of simultaneous heart sounds, jugular pulse and lead II. Here retrograde P waves are found also to be followed by a high "a" wave in the jugular pulse. When the jugular pulse "a" wave is absent, it can be seen that the preceding retrograde P wave had been blocked probably due to an increasingly fatigued A-V node. The corresponding alternation in the heart sounds (Fig. 3B) is noted; this figure therefore displays increasing QRS-P intervals (i.e., increasing time intervals from preceding QRS to initial downstroke of retrograde P wave) representing increasing retrograde conduction time through the A-V node. When the A-V node is so fatigued that the retrograde impulse is not conducted through from ventricle to auricle, the retrograde Wenckebach effect occurs. Whenever the retrograde P wave appears, the sinus node is discharged so that no evidence of sinus activity will be detected. However, if the sinus discharge occurs at a time when the auricle is not refractory, the sinus P wave will be seen in lead II as an upright wave superimposed on the T wave. This establishes the definitive diagnosis of ventricular tachycardia. In Figure 4B (April 23, 1948) simultaneous heart sounds, radial pulse and lead II are recorded. This shows also the presence of both retrograde P waves and sinus P waves. Here we find that both retrograde P waves and sinus P waves had a definite effect on the following systole in that the amplitude of the following S1 is always increased. However, there appears to be no constant relationship between preceding auricular activity and the amplitude of the radial pulse beat; the marked pulsus alternans is quite apparent and accounts for the pulse deficit at the wrist. Dr. Simon Dack of the Cardiographic Department was the first to note the increasing retrograde A-V node conduction time plus retrograde Wenckebach effect and supported this contention by means of an electrokymogram. Figure 5 represents a record which includes simultaneous heart sounds, lead II, jugular pulse and electrokymogram taken over the right auricle with the patient recumbent. If one follows a time line directly above the letter Y, the results of a retrograde P wave on the various components studied are seen. Following such a time line we see that a retrograde P wave gives rise to an early accentuated S1 (first heart sound), a high "a" wave in the jugular pulse and a presystolic downward deflection of the electrokymogram beam indicating right auricular systole. If a time line above the letter X is followed, we see that the retrograde P wave has been blocked; and as a result of this there is a later, lower amplitude S1, an absent "a" wave of the jugular pulse and an absence of the downward deflection in the electrokymogram beam indicating absent auricular systole. This offered graphic proof that the inverted

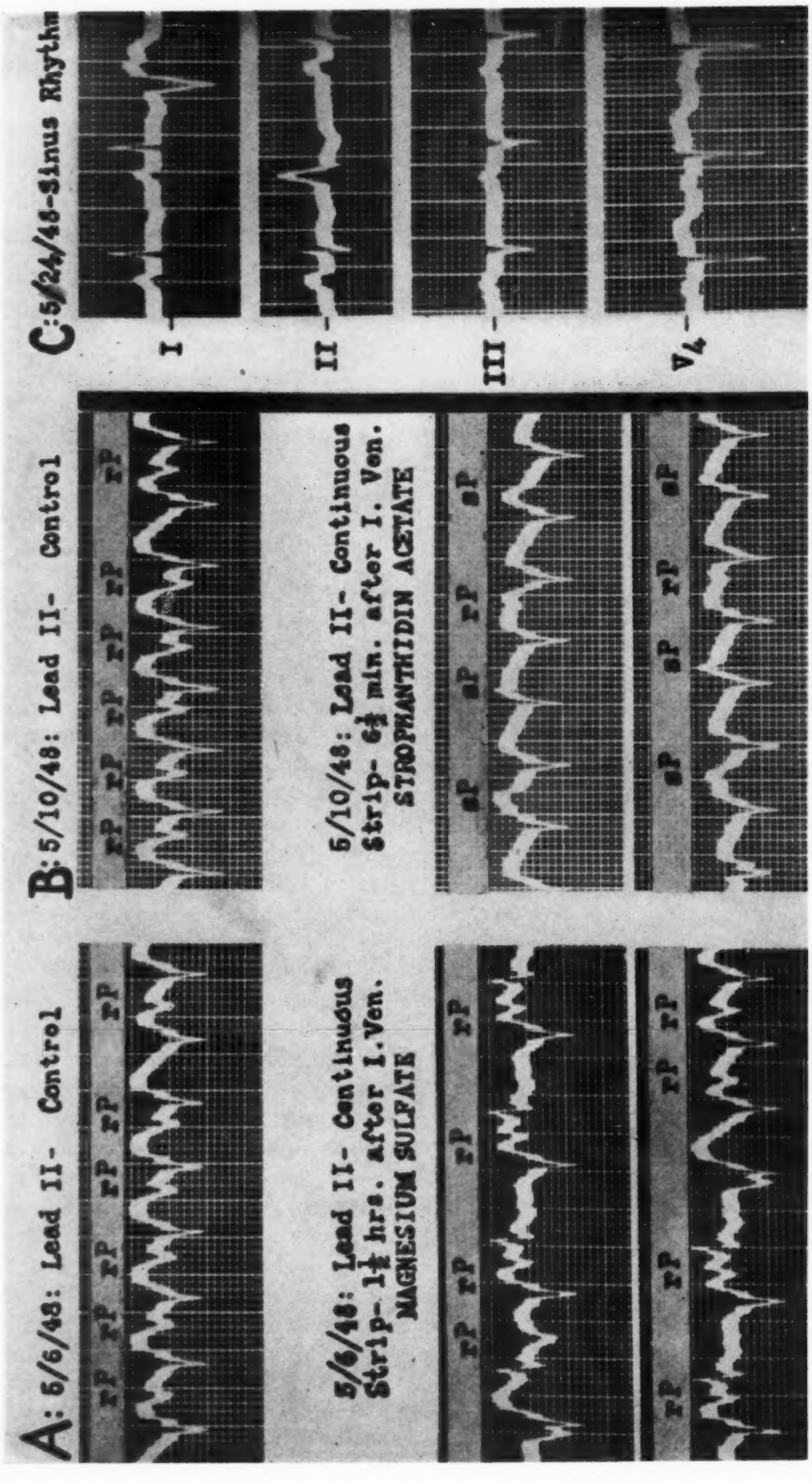

FIG. 6. A, Lead II control showing ventricular tachycardia with retrograde P waves plus Wenckebach effect. Continuous strip one and a half hours after intravenous $MgSO_4$ shows appearance of bigeminy with rhythmic alternation in the direction of the QRS complexes and then return to original rhythm. rP = retrograde P and sP = sinus P waves. B, Lead II control showing ventricular tachycardia with retrograde P waves plus Wenckebach effect. Continuous strip six and a half minutes after intravenous strophanthidin acetate shows flattening of T waves and appearance of separate sinus rhythm (upright P waves) plus retrograde and blocked P waves. C, restoration of sinus rhythm plus multifocal ventricular premature beats; deep Q and elevated RS-T in Lead V_4 plus inverted T_I and II and flat T_{III}—representing persistent changes of old anterior wall infarction. (Fig. 1.)

deflections on the T waves of the electrocardiogram were definitely retrograde P waves and that a true retrograde Wenckebach effect existed.

Figure 6A shows the effect of intravenous magnesium sulfate (10 cc. of a 25 per cent solution). Control tracing (lead II) shows ventricular tachycardia with retrograde P waves exhibiting a Wenckebach effect. Continuous strip taken at one and a half hours after the intravenous magnesium sulfate shows the appearance of bigeminal rhythm with alternation in the direction of the QRS complexes followed by return to the control rhythm. This "second focus" appears premature and is similar in configuration to the QRS noted during a paroxysm of ventricular tachycardia on September 12, 1947 (Fig. 2B, lead II), and also to the QRS in lead II after restoration of sinus rhythm. (Fig. 6C.) This episode of bigeminy may therefore represent a "re-entry" phenomenon.

Figure 6B shows the effect of intravenous strophanthidin acetate. The control tracing (lead II) shows ventricular tachycardia with retrograde P waves exhibiting a Wenckebach effect. Continuous strip, taken six and a half minutes after intravenous injection of 1 mg. of strophanthidin acetate, shows flattening of the T waves and the appearance of separate sinus (upright) P waves plus retrograde and blocked P waves.

In this continuous strip the upright sinus P waves appear superimposed upon the T waves and occur at a rate of 98 per minute. The retrograde (inverted) P wave when present discharges the sinus node prematurely with the result that the next succeeding sinus P wave cycle occurs earlier. This absence of a full compensatory pause is analogous in sinus rhythm to the effect of an auricular premature beat on the earlier timing of the next succeeding sinus impulse.

Figure 6C shows the restoration of regular sinus rhythm plus multifocal ventricular premature beats. The inverted T in I and II, isoelectric T in III, deep Q wave and elevated RST segment in lead V_4 represent the persistent changes of previous anterior wall infarction. It is noted that this sinus rate is the same as the rate of the sinus (upright) P waves in the previous records exhibiting the ventricular tachycardia.

COMMENTS

Sir Thomas Lewis in 1909 published the first case of ventricular tachycardia with analysis by electrocardiographic, radial and venous pulse tracings.[12] Since that time numerous cases have been reported, several of which were of prolonged duration,[1–8,17] the longest recorded continuous paroxysm being one of 123 days.[4] As pointed out by Levine[13] the presumptive diagnosis of paroxysmal ventricular tachycardia may be made clinically according to the following findings: (1) a rapid, essentially regular rhythm with slight irregularities; (2) some variation in the intensity of the first heart sound; (3) failure of vagal stimulation to slow the heart rate. Kymography has been utilized as a diagnostic aid by Kahlstorf;[14] in our case electrokymography provided corroborative evidence for the unusual auricular activity during the paroxysm of ventricular tachycardia.

The exact diagnosis may be established by the following electrocardiographic criteria:[7,15–18] (1) a paroxysm of three or more abnormal ventricular complexes at a rapid rate with the duration of the QRS equal to or greater than 0.12 second; the occurrence of P waves at a rate independent of the ventricular rate during the paroxysm (unless retrograde auricular stimulation or auricular fibrillation is present); (2) close resemblance of ventricular premature beats to the QRS complexes occurring during the paroxysmal tachycardia; (3) timing of the first beat of the paroxysm premature with respect to the normal rhythm and possibly a full compensatory pause following the last beat of the paroxysm. A-V nodal tachycardia in the presence of intraventricular or bundle branch block produces an electrocardiographic pattern often indistinguishable from that of ventricular tachycardia.

Williams and Ellis[17] in an analysis of about 64,000 routine electrocardiograms taken over a twenty-year period at the Boston City Hospital found ventricular tachycardia in thirty-six cases, an incidence of 1:1,800 tracings. Organic heart disease was present in all but one instance. Digitalis toxicity was considered the precipitating factor in eight cases and the probable factor in nine more; myocardial infarction was

definitely associated with six cases and probably with three others. Of twenty-seven cases reported by Cooke and White[7] twenty patients had coronary heart disease and in at least five cases digitalis was considered the chief etiologic factor. Master and his associates[19,20] found only one instance of paroxysmal ventricular tachycardia in 300 cases of acute coronary artery occlusion studied at the Mount Sinai Hospital. Others record an incidence of about 1 to 3 per cent for the occurrence of this arrhythmia in acute coronary artery occlusion.[21,22] The arrhythmia occurs also in chronic cases of myocardial damage secondary to coronary arteriosclerosis. In both acute and chronic coronary heart disease the arrhythmia is probably related to ischemic foci in the ventricular musculature although several workers believe that the stimuli arise in the bundle of His or main branches. Paroxysmal ventricular tachycardia occurs rarely in the absence of organic heart disease.[3,17,23–25] In fact, attacks have been related to changes in posture alone.[26] In the field of general anesthesia paroxysmal ventricular tachycardia has been encountered not infrequently especially during thoracic surgery.[27] Cooke and White[7] combining their figures with those of Strauss[28] showed the age incidence of paroxysmal ventricular tachycardia to be greatest during the sixth decade of life; the arrhythmia is found statistically to be more frequent in men.

The symptoms and signs of paroxysmal ventricular tachycardia are quite varied and will depend upon such factors as the etiologic agent, cardiac rate, heart size, presence of acute myocardial damage and / or circulatory failure. There may be merely the subjective sensation of palpitation. At the other extreme the patient may be in shock with marked pallor, inaudible heart sounds and severe hypotension. Faintness or actual syncope occasionally are prominent symptoms.[29] The latter may be directly attributable to the decreased minute volume output of the heart which has been shown to be reduced by as much as one-third of the normal.[30] The duration of the arrhythmia varies from runs as short as three successive abnormal ventricular beats to continuous attacks as long as 123 days.[4]

The usual type of paroxysmal ventricular tachycardia recorded electrocardiographically has been described herein; the P waves may be seen independent of and superimposed upon the QRS and T waves. In the more serious cases there may be rhythmic bidirectional alternation of the ventricular complexes[31–35] and, more rarely, this electrical alternans may be unidirectional.[36,37] The auricular rhythm is usually normal and independent but concomitant auricular tachycardia, flutter or fibrillation may be present.

In the event of retrograde auricular stimulations,[6,16,37–39] increasing fatigue of the A-V node will result in a retrograde Wenckebach effect. When retrograde auricular stimuli occur, they may discharge the sino-auricular node. Whether one finds sinus, retrograde or fusion P waves depends upon the respective timing of the two foci. Following a bout of paroxysmal ventricular tachycardia the electrocardiogram may reveal marked RS-T and T wave abnormalities and QT interval prolongation persisting for as long as several weeks.[3,40–44]

Since the prognosis of patients with paroxysmal ventricular tachycardia is generally poor and the danger of severe congestive failure and of ventricular fibrillation ever present, prompt therapy is urgent. Quinidine remains the drug of choice and should be administered in increasing doses and by all routes before resorting to other therapy. Experimentally in dogs one large oral dose results in maximal concentration in the myocardium in about one hour and is eliminated from the heart in about seven hours.[45] Several reports of the use of massive doses of quinidine orally in this condition are found in the literature[46,47] and Levine[22] mentions the administration of 112 gr. in one day with reversion to normal rhythm. Many workers support the use of such large doses of quinidine and do not believe that it is detrimental even following acute coronary artery occlusion.[48–50] With parox-

ysmal ventricular tachycardia quinidine therapy causes slowing of the ventricular rate (which in itself results in improvement of the circulation),[2,17] prolongation of the QT interval and widening of the QRS complex. Good effects have been obtained by continuing large doses despite the onset of cinchonism or excessive widening of the QRS interval.[48,51] However, because of the danger of ventricular fibrillation and cardiac standstill with quinidine overdosage,[52,53] Reich[47] advocates cessation of quinidine therapy when the QRS width becomes increased by more than 25 per cent.

For a fair trial of oral quinidine therapy the following schedule is recommended: After the customary test for idiosyncrasy using 3 gr. of quinidine sulfate by mouth one should commence with oral dosage of 6 gr. every two hours, if ineffectual 6 gr. every hour, and finally, if necessary, 9 gr. every hour. The total quantity given for any one clinical trial will depend upon the condition of the patient, the exhibition of cinchonism and the appearance of marked electrocardiographic disturbances attributable to the drug. The recommended total dosage for a single clinical trial varies from about 3 to 10 gm.[38]

In the event of failure by the oral route quinidine or its levoisomer, quinine, should then be administered intramuscularly using one of the following: Quinine dihydrochloride may be tried in doses of 0.5 gm. repeated every two hours.[54] Quinidine sulfate has also been used intramuscularly in doses of 0.4 gm. every four hours for two or three doses.[38] Finally, if intramuscular administration fails one must resort to the intravenous route. Schwartz and Jezer[52] noted that intravenous quinine dihydrochloride or quinidine sulfate resulted in either a prefibrillatory mechanism or actual transient periods of ventricular fibrillation in their cases. Cardiac standstill with death may also be a direct result.[55] Nevertheless, occasion often necessitates the intravenous route and favorable termination of the paroxysm not infrequently follows intravenous quinine or quinidine.[1,8,34,56–58] Quinine dihydrochloride may be used by intravenous injection in doses of 0.5 gm. in 5 cc. solution[54] or may be administered in more dilute solution by intravenous drip. Quinidine sulfate for intravenous use[58] may be prepared by dissolving 50 to 60 gr. in 500 cc. of 5 per cent glucose, filtering the solution and then administering 100 to 120 cc. per hour after warming the filtrate slightly. Because of its greater solubility quinidine lactate may be preferable as the intravenous agent. It is available for experimental use in 0.65 gm. ampules in 10 cc. of saline (Lilly). It should be re-emphasized that when given intravenously these drugs must be administered quite slowly and with great caution because of the aforementioned dangers. Following reversion to normal rhythm oral doses of quinidine should be maintained for prolonged periods.

Atabrine (quinacrine hydrochloride) has a protective action against ventricular fibrillation induced experimentally by adrenalin in anesthetized dogs receiving chloroform.[59] Although Gertler and Yohalem[60] have found 0.6 gm. doses of atabrine intramuscularly to be ineffective against paroxysmal ventricular tachycardia, this drug deserves trial in refractory cases and especially in those showing intolerance or idiosyncrasy to quinidine.

Despite the adverse electrocardiographic changes and alterations in rhythm which have been described during the use of potassium salts in therapeutic doses,[61] this drug has been found successful when given alone or in combination with quinidine.[62,63] The recommended dose is 1 to 2 gm. of potassium chloride or acetate orally every two to four hours until a favorable response is obtained. Magnesium salts have been used in paroxysmal ventricular tachycardia with occasional favorable results explained by a greater selective depressant action upon ectopic centers than on the normal conducting mechanism.[64] Moderately rapid intravenous injection of 15 to 20 cc. of a 20 per cent solution of magnesium sulfate has been recommended; larger amounts in

lower concentration are claimed to be less effective.[65]

Intravenous administration of 10 to 40 mg. of morphine sulfate has been reported[66] to cause cessation of the attack of paroxysmal ventricular tachycardia in nine of ten cases; the interval between doses was one-half to two hours. Herrmann and Hejtmancik[56] also reported success with intravenous morphine in one instance after a ¼ gr. dose and in another case on carotid sinus pressure six minutes after a ¾ gr. dose. Although attempts at increasing vagal tone by carotid sinus pressure and by drugs such as mecholyl (acetyl β-methyl choline) are usually ineffective,[67] carbachol (carbamino choline chloride), a cholinergic drug, was reported to be curative in a slowly injected intravenous dose of ⅛ mg. in 5 per cent saline.[68] Atropine sulfate was found to cause disappearance of the arrhythmia in one case following a single dose of 2 mg. (1/30 gr.);[69] in this unusual instance complete heart block was uncovered. Experimentally in animals bilateral vagotomy broke epinephrine-induced paroxysmal ventricular tachycardia[70] and intravenous atropine prevented its induction by epinephrine. The vagolytic action of atropine results in an increase of sinus rate and permits recapture of control by the sinus node when its rate exceeds that of the ventricular pacemaker.[71] Therefore, the use of a large dose of atropine sulfate parenterally in paroxysmal ventricular tachycardia after partial slowing of the rate by quinidine seems worthy of further clinical trial.

The work of Burstein et al.[9,27] using intravenous procaine heralds a new approach to the therapy of paroxysmal ventricular tachycardia. This has been found to be exceedingly effective in cases occurring during anesthesia when given in doses of 5 to 10 cc. of 1 per cent procaine intravenously. The convulsant side effect of intravenous procaine in conscious patients has limited its use in the type of paroxysmal ventricular tachycardia encountered clinically; however, prior barbiturate narcosis may obviate this difficulty. Papper et al.[72] found diethylaminoethanol, a hydrolytic product of procaine, to be less toxic than its parent substance. Rosenberg et al.[10] reported that this newer drug controlled the arrhythmia in six of eight cases in total doses of from 4.5 to 9 gm. intravenously; the case being reported herein represents one of the failures. Although diethylaminoethanol may be safely administered intravenously to the unanesthetized patient, its relative instability in the body and hypotensive action confine its use. A newer, more stable and less toxic drug, the amide of procaine, has been studied extensively by Mark et al.[73] and has recently been made available commercially.* The reported distinct advantages include safety of administration to both conscious and anesthetized patients as well as effectiveness by the oral route. The dose recommended for the treatment of paroxysmal ventricular tachycardia with procaine amide is 0.25 to 0.5 gm. every four to six hours orally or 200 to 1,000 mg. intravenously. In conscious patients the intravenous injection should be made slowly, under electrocardiographic control and with frequent checks for any hypotensive effect. Should further clinical experience with this drug substantiate the lower toxicity and effectiveness in cases refractory to quinidine,[73] procaine amide may replace the latter as the drug of first choice for the therapy of this condition.

Digitalis, itself often the cause of paroxysmal ventricular tachycardia, is usually contraindicated in the treatment of this arrhythmia; however, if cardiac failure ensues, digitalization may be necessary. Several authors have minimized the danger of digitalis in this condition even when administered with quinidine[51] and have advocated this combination in full dosage for its complete control.[7,56] Papaverine, too, has been advocated for paroxysmal ventricular tachycardia; Katz[38] recommends doses of 1½ gr. intravenously. Ergotamine controlled a case of the orthostatic type[26] presumably by its sympatholytic action.

* This product is called Pronestyl Hydrochloride and is manufactured by Squibb.

Extension of present experimental work along this line using other sympatholytic agents such as dihydroergotamine and dihydroergocornine[74] and dibenamine®[75] may lead to further clinical application. Finally, stellectomy[38] has been performed in resistant cases of this arrhythmia as a last resort.

SUMMARY AND CONCLUSION

1. A case of paroxysmal ventricular tachycardia, unusual for its duration (fifty-seven days) and for the presence of retrograde Wenckebach effect, is reported in detail.

2. The various methods now available for the therapy of this arrhythmia are discussed.

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Pulmonary Infiltration with Blood Eosinophilia*

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JUDGING from the recent literature the combination of pulmonary infiltrations with blood eosinophilia is a more protean disease than is commonly believed. Loeffler's syndrome and tropical eosinophilia are the two classic syndromes which have been described, principally in the foreign literature. Recently several variants have been reported.[1,2] Occupying an intermediate position the following case bears resemblances to each of these syndromes in certain aspects yet it is characteristic of neither.

CASE REPORT

A forty-eight year old Swedish cook complaining of malaise and fever was admitted to the medical wards of St. Luke's Hospital on December 5, 1947. The patient was well until two weeks before admission when she noted the onset of a moderate non-productive cough and left anterior chest pain which was aggravated by the cough. These symptoms were associated with fever and malaise. Two or three days after onset the chest pain disappeared. The other symptoms continued and because of failure to improve she remained in bed for the week preceding admission.

There was no history of tuberculosis in her family or of contact with tuberculosis. She stated that she never had pneumonia, pleurisy, asthma or hayfever. In July, 1947, while in Maine she had a mild upper respiratory infection, and because it was followed by a cough which persisted for a week or two, she was advised to have a chest x-ray at the local hospital. This roentgenogram was obtained by us and found to exhibit no abnormal findings.

Physical examination disclosed a well nourished, well developed white female whose skin was warm and moderately flushed. The rectal temperature was 100.4°F., pulse 110, respiratory rate 20 and blood pressure 118/78. Funduscopic examination revealed minimal arteriosclerotic changes of the retinal arterioles. The nasopharynx was slightly injected. The remainder of the physical examination was completely negative.

Urinalysis was completely negative. The hemoglobin was 12.4 gm. (85 per cent) with 4.4 million red blood cells. The white blood cells numbered 11,450 with 80 per cent neutrophiles and 20 per cent lymphocytes. There was a marked left shift of the neutrophiles. The sedimentation rate (Westergren) was 75 mm per hour. The Mazzini reaction was negative. The blood urea nitrogen was 10.1 mg. per cent and the blood sugar 99 mg. per cent. The initial electrocardiogram was not remarkable. A postero-anterior roentgenogram of the chest revealed a mottled increase in density in the right lower lung field and a similar irregular density in the left lung field adjacent to the lung root. A lateral x-ray demonstrated that these areas occupied the right middle lobe and the apex of the left lower lobe.

A detailed chronologic account of this patient's illness during her hospitalization of 175 days would be pointless since there was essentially no change in her clinical state until the last three weeks. For over five months she presented a stationary clinical picture, the chief objective signs of which were low grade fever, widespread shifting pulmonary infiltrations and a marked eosinophilia. At no time was she acutely ill. Her complaints were of a relatively minor nature. She rarely coughed and raised practically no sputum. Occasionally there were vague abdominal complaints which responded well to symptomatic treatment. Other than these minor complaints she was virtually asymptomatic.

Serial roentgenographic studies of the chest

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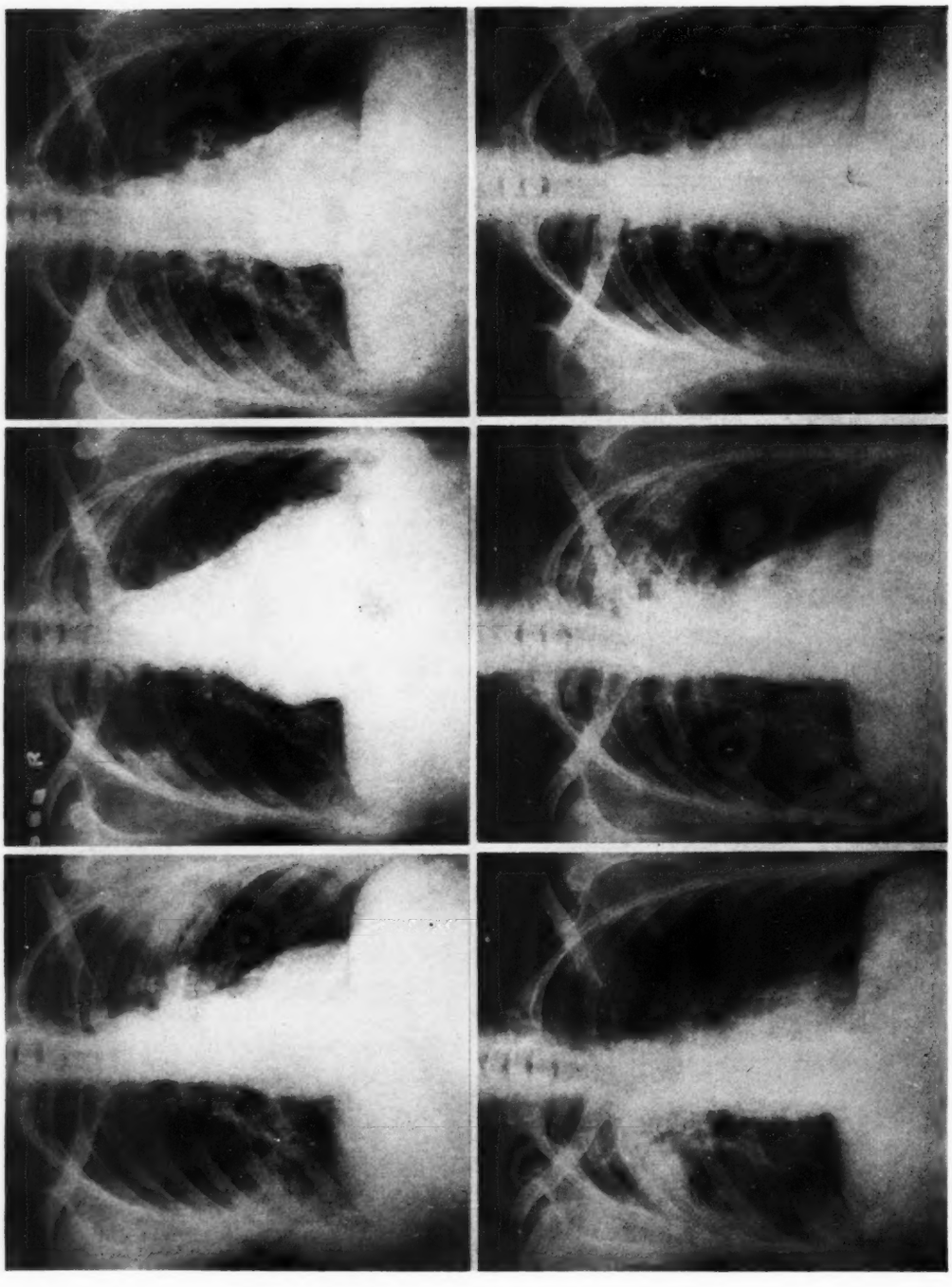

FIG. 1. Serial films dates as follows: A, December 6, 1947; B, January 21, 1948; C, February 24th; D, April 16th; E, May 14th; F, June 22nd. These demonstrate the multiple, bilateral shifting areas of pulmonary parenchymal infiltrations as described in the text. Noteworthy is the moderate, generalized cardiac enlargement present in B, with return to normal cardiac size in subsequent films.

revealed persistent, extensive infiltrations of the lung parenchyma which shifted throughout the lung fields in a haphazard way. At one time or another practically every portion of both lung fields was involved. The infiltrations were principally mottled in appearance and amazingly deceptive in that, despite frequently alarming roentgenographic changes, the patient presented a dearth of physical findings. Occasionally, faint moist rales were heard and at one time diminished resonance developed at the left base. In general, on most occasions the lungs were clear to percussion and auscultation. Photographic reproductions of representative chest x-rays demonstrating the shifting character of the pulmonary lesions are shown in Figure 1.

As indicated in Table 1 the patient had a persistently elevated temperature which was not influenced by a variety of therapeutic measures. Adequate trials with full therapeutic dosages of sulfadiazine, penicillin and streptomycin elicited no discernible beneficial effect. Beginning February 4, 1948, neoarsphenamine 0.3 gm. was given twice a week for two weeks with no effect. A variety of antihistaminic drugs (pyribenzamine, benadryl, thephorin) was given with no demonstrable alteration in the course of the illness. On January 22 and 23, 1948, roentgeno-

TABLE 1

Date 12–6–47	Temperature °F. (rectal)	White Blood Cells/mm.^{3}	Neutrophiles (Per cent)	Lymphocytes (Per cent)	Monocytes (Per cent)	Basophiles (Per cent)	Eosinophiles (Per cent)	Erythrocyte Sedimentation Rate (mm./hr.)	Weight (lbs.)
12–6–47	101.6	11,450	80	20				75	
12–8–47	101.8	12,050	78	18	4				138
12–11–47	100.4	12,700	68	13	1	2	16	80	
12–15–47	100.8	19,500	64	10	2		24		137½
12–22–47	101.0	18,000	37	17	4		42		132
12–29–47	101.0	14,900	34	15	1		50	42	135
1–5–48	101.0	22,000	25	13	2	1	59		138½
1–12–48	101.8	19,200	41	23	2		34	52	134½
1–19–48	100.0	13,800	38	23	2		37		129
1–26–48	100.8	12,000	48	17	2		33	55	129
2–2–48	100.4	11,500	44	20	6		30		128
2–9–48	100.0	15,700	30	24	2		44		127½
2–16–48	99.8	14,900	14	23			63	63	128½
2–24–48	101.2	13,000	22	17		3	58	55	129
3–1–48	101.6	12,400	18	14	4	1	63		128
3–6–48	99.8	13,900	23	24		2	51	64	
3–15–48	99.6	19,000	36	25	2		37		128
3–22–48	100.6	17,000	51	17			32		129½
3–29–48	100.6	13,000	50	18	2		30	56	129
4–5–48	102.8	15,300	49	19	4		28		130
4–12–48	101.0	14,500	43	27	2		28		
4–19–48	100.4	13,200	54	14	2		30		131
4–26–48	101.0	13,000	48	16			36	70	133
5–3–48	100.2	17,000	48	17	5		30		133¼
5–10–48	99.8	13,400	50	17	4		29		
5–17–48	100.0	11,800	30	32	1		37	54	
5–24–48	100.0	10,800	43	22	7		28	52	135
5–28–48	Discharged to Convalescent Hospital (5–28–48 to 6–18–48).								
Outpatient Department Follow-up									
6–24–48	98 (orally)	9,000	57	30	4		9		144½
7–21–48	98.6 "	7,850	52	35	7		6		147¾
1–6–49	98 "	6,900	63	30	6		1		157¾

grams of the chest preceding and following the injection of adrenalin, according to the method of Blanton,[3] failed to demonstrate any appreciable change in the character of extent of the pulmonary infiltrations.

Also tabulated are leukocyte counts with differential analyses of the smears. The percentage of eosinophiles mounted rapidly and reached 63 per cent on the seventy-third and eighty-eighth day. The sedimentation rate was persistently elevated and showed no directional trend.

On serial study the electrocardiographic pattern, which was normal on admission, underwent a series of moderate changes in the ST segments and T waves. These alterations, principally a flattening of the T waves in the limb leads, inversion of Tcf[4] and slight depression of ST segments in all leads, developed after the first week and were still present at the time of discharge. Some improvement was noted on May 11, 1948, sixteen days before the patient was transferred to the Convalescent Hospital.

Exhaustive attempts to determine the etiology of the illness were futile. On seven occasions blood cultures, using various media, grew no pathogens. On January 3, 1948, examination of the sputum revealed numerous eosinophiles. Again on February 2, 1948, and on April 17, 1948, eosinophiles were found in the sputum. Sputum concentrates on many occasions were negative for tubercle bacilli. Tubercle bacilli could not be found in the gastric contents or could they be cultured. Tuberculosis could not be demonstrated by guinea pig inoculation with sputum material. Pathogenic fungi could not be cultured from the sputum. Nose and throat cultures revealed Neisseria catarrhalis, Streptococcus viridans and Staphylococcus aureus hemolyticus. Numerous stool specimens were negative for ova and parasites.

The Mazzini test, initially negative, did not turn positive as the illness progressed. Agglutination tests for typhoid, parathyphoid, brucella and proteus organisms were negative. Intradermal tests with brucella and trichinella antigens were negative. Serial intradermal tests with old tuberculin beginning at a 1:100,000 dilution were negative with increasing concentrations until the 1:100 dilution was reached; at this point a 1+ reaction was obtained.

On January 12, 1948, in order to rule out trichinosis and periarteritis nodosa, a biopsy of skin, subcutaneous tissue, facia and muscle was taken from the right thigh. Microscopic examination of the tissue failed to reveal any abnormalities.

Extensive allergic studies were made and no positive reactions resulted from testing with the common inhalant protein extracts, pollens, common fungus extracts and several series of food tests. The only intradermal tests considered positive were reactions to a strain of Str. viridans cultured from the sputum and two organisms (Escherichia coli and Staph. aureus hemolyticus) which were cultured from maxillary sinus washings. Accordingly, there was prepared an autogenous treatment vaccine containing 10 units (Famulener) of each of the three organisms to which she reacted.

Treatment was begun on March 23, 1948, with 300 m.u. of this vaccine and increasing doses given at approximately weekly intervals until a dose of 3,500 m.u. was reached on May 25th. At this point treatment was discontinued. Since there had been no reaction to any of the common allergens, it was thought desensitization to histamine would be of benefit. Consequently, on April 15th 0.066 mg. of histamine diphosphate was given and the dosage increased at approximately weekly intervals until a level of 0.54 mg. of histamine diphosphate was reached on May 20th. Only two additional injections of histamine diphosphate were given after this point before treatment was discontinued.

In the last three weeks of her hospitalization prior to her transfer to the Convalescent Hospital there was a marked subjective improvement. This was accompanied with a moderate drop in temperature to a point which averaged slightly over 99°F. The appearance of the chest film improved noticeably; infiltrations were still present on discharge but were of lesser degree.

She remained at the Convalescent Hospital from May 23rd to June 18, 1948. During this period she continued to improve and was afebrile. The infiltrative pulmonary process continued to improve and on June 22nd, four days after her discharge from the Convalescent Hospital, no definite areas of infiltrations were seen. Follow-up films on July 21, 1948, and January 6, 1949, revealed no recurrence of the parenchymal infiltration. In follow-up visits at the clinic there was a progressive decrease in total leukocyte count and eosinophilia, falling from 9,000 white blood cells with 9 per cent eosinophiles on June 24, 1948, to 6,900 white blood cells with 1 per cent eosinophiles on January 6, 1949.

COMMENTS

Following Loeffler's original description[4] of the syndrome which bears his name, numerous reports appeared, chiefly in the European literature. In 1940 Freund and Samuelson[5] collected 105 cases; fifty-one of these cases were reported by Loeffler himself.[6]

For some reason the disease appears to be relatively rare in this country. As recently as 1945 Miller,[7] reporting a case of Loeffler's syndrome of unknown etiology, could find only four cases reported in the American literature.

Roentgenographically, the most characteristic finding is the presence of abnormal shadows of a transient nature which shift in position throughout the lung fields. These may be large or small, irregular or circular, unilateral or bilateral, and homogeneous or mottled. At times lesions which mimic the adult form of pulmonary tuberculosis may be found.

Invariably the course is benign with complete resolution of the pulmonary shadows within three to eight days. Symptoms remain relatively minor and disappear in a few days.

Usually leukocytosis is not striking, occasionally reaching 15,000. Differential analysis of the white blood cells usually reveals 10 to 50 per cent eosinophiles. The degree of eosinophilia cannot be correlated with the extent of the pulmonary infiltrations.

Although exact mechanisms are by no means understood, it is now conceded by practically all authorities that the etiology of Loeffler's syndrome is allergic in nature. The various agents are adequately discussed in a recent report.[1]

Tropical eosinophilia (eosinophilic lung, pseudotuberculosis associated with eosinophilia) has been the subject of numerous reports in the Indian literature[8–13] in addition to reports in the English and American literature.[14,15] The gradual onset is chiefly characterized by malaise, anorexia and fever. A dry, hacking cough soon becomes a prominent symptom. Wheezing and expiratory dyspnea occur. The total leukocyte is usually over 20,000 per cu. mm. and may reach 80,000 per cu. mm. Massive eosinophilia, the most characteristic feature of this syndrome, is responsible for the leukocytosis. Absolute numbers of neutrophiles and lymphocytes are unchanged. Roentgen examination of the chest during the febrile period usually reveals a characteristic, widely disseminated mottling of both lung fields. The mottling is usually most pronounced at the end of the second week of the illness and rarely lasts more than four weeks.[14]

The course of the illness is extremely variable. Usually after several weeks the temperature returns to normal. Paroxysmal coughing and asthmatic episodes may become chronic in many patients. The disease may last from several weeks to as long as five years. Whether begun early or late in the course of the illness a dramatic response to organic arsenical therapy is the rule.

The etiology of tropical eosinophilia is obscure. Various infestations have been described in association with this syndrome, but none has been consistently present. Because of the eosinophilia and asthmatic component so frequently observed the possibility of an allergic mechanism has been discussed by several authors, but no definite evidence has been offered. Cartwright,[2] in contrasting the salient characteristics of tropical eosinophilia with Loeffler's syndrome, states, "Actually these are differences only in degree and it is debatable whether tropical eosinophilia and Loeffler's syndrome are different diseases."

In common with Loeffler's syndrome the case presented showed a benign, almost asymptomatic course, a paucity of physical findings and shifting pulmonary infiltrations. The protracted course, low grade fever and considerable eosinophilia would prompt one to relate the syndrome described with tropical eosinophilia. However, the characteristic x-ray findings of tropical eosinophilia are lacking. In addition, the paroxysmal cough and asthmatic features

of tropical eosinophilia are absent. Finally, failure to respond to organic arsenical therapy would tend, according to most authorities, to rule out the diagnosis of tropical eolsinophiia.

No definite conclusion can be drawn regarding the effects of the administration of the prepared bacterial vaccine. All that can be said is that after extensive investigation attempts at desensitization were made with the only substances to which she reacted and that this treatment was begun approximately six weeks before definite improvement was noted. Obviously, no valid causal relationship could be established in a single case. However, the employment of desensitization technics could be appraised in the future when similar cases are investigated.

Rather than attempt to fit this clinical syndrome into any classic symptom complex, it is probably wisest to adhere to the proposal of Ham and Zindahl[1] who suggest that "the cases which fit into the initial symptom complex should be called Loeffler's syndrome but that all other cases should be termed pulmonary infiltration with blood eosinophilia with an unknown or known etiological factor." Consequently, until further investigation into this field provides us with greater knowledge, it is probably best to include this clinical syndrome in the group of "pulmonary infiltrations with blood eosinophilia, unknown etiology."

SUMMARY

1. A case of chronic pulmonary infiltration with blood eosinophilia of unknown etiology is presented.

2. Similar cases are relatively rare in the American literature and etiologic mechanisms are poorly understood.

3. Loeffler's syndrome and tropical eosinophilia, two diseases which bear certain similarities to this clinical syndrome, are discussed.

4. Further investigation is needed not only to clarify the etiology of this syndrome but also to determine the role of arsenicals, antihistaminic drugs and desensitization technics as therapeutic agents.

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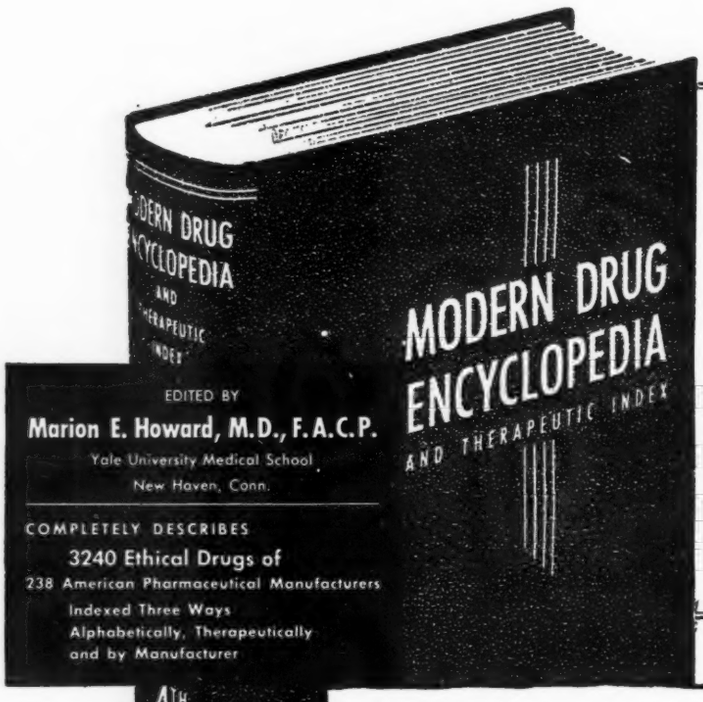

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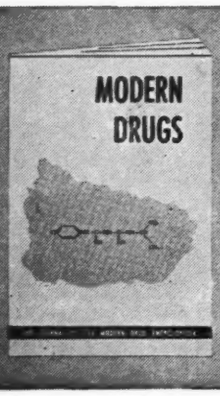

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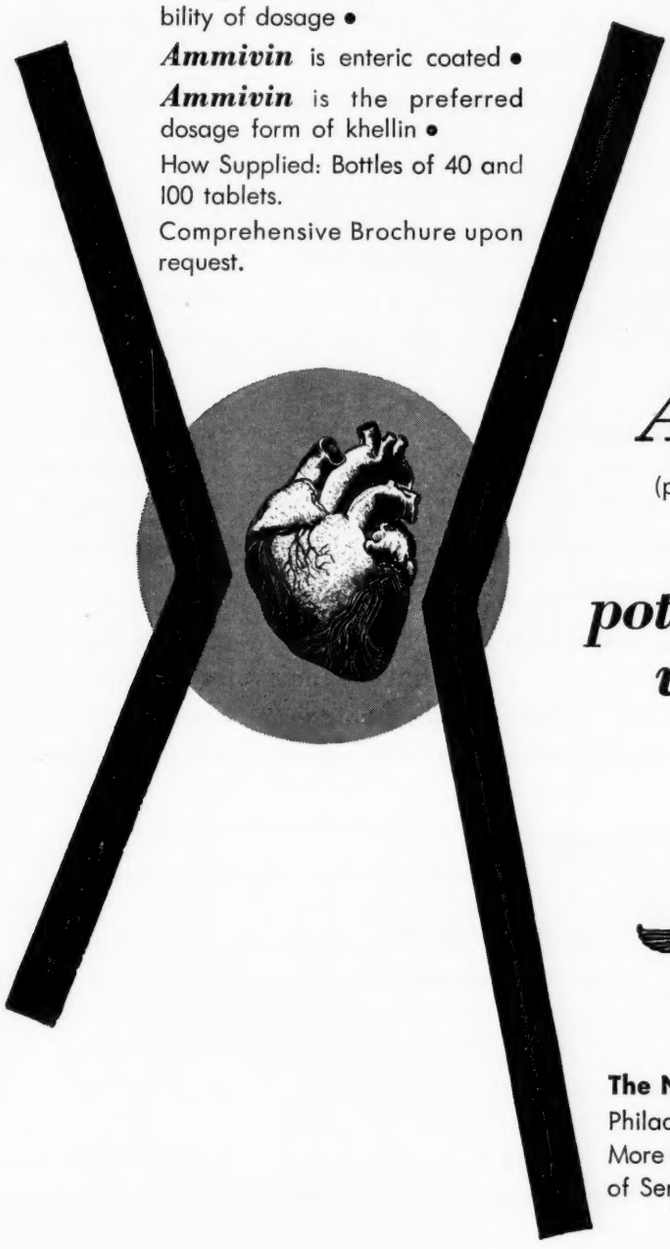

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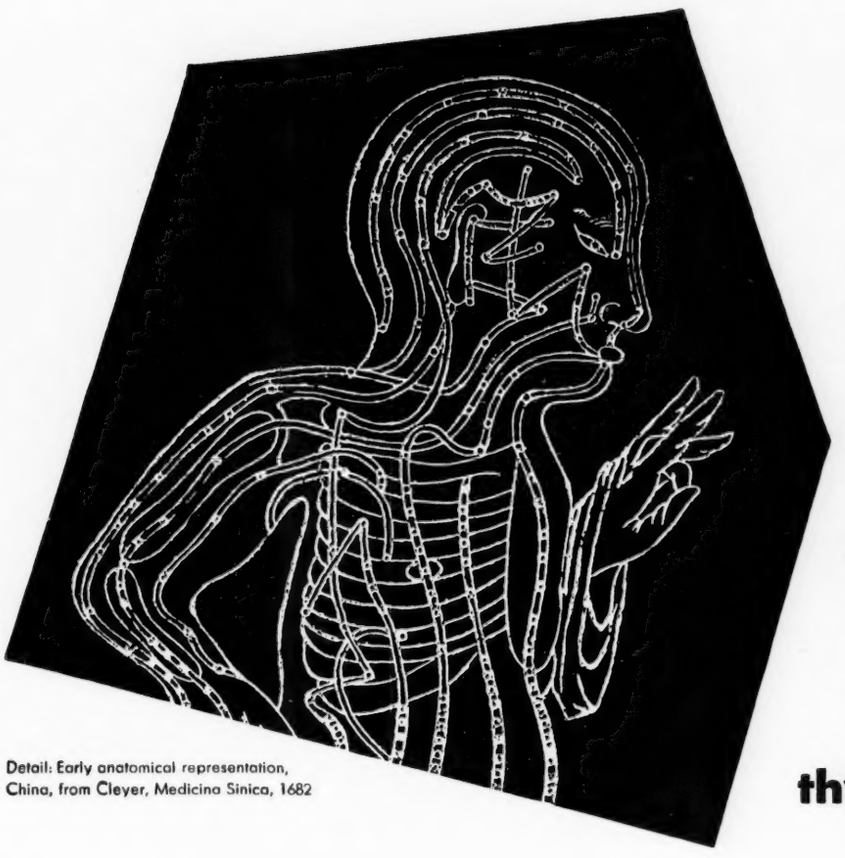

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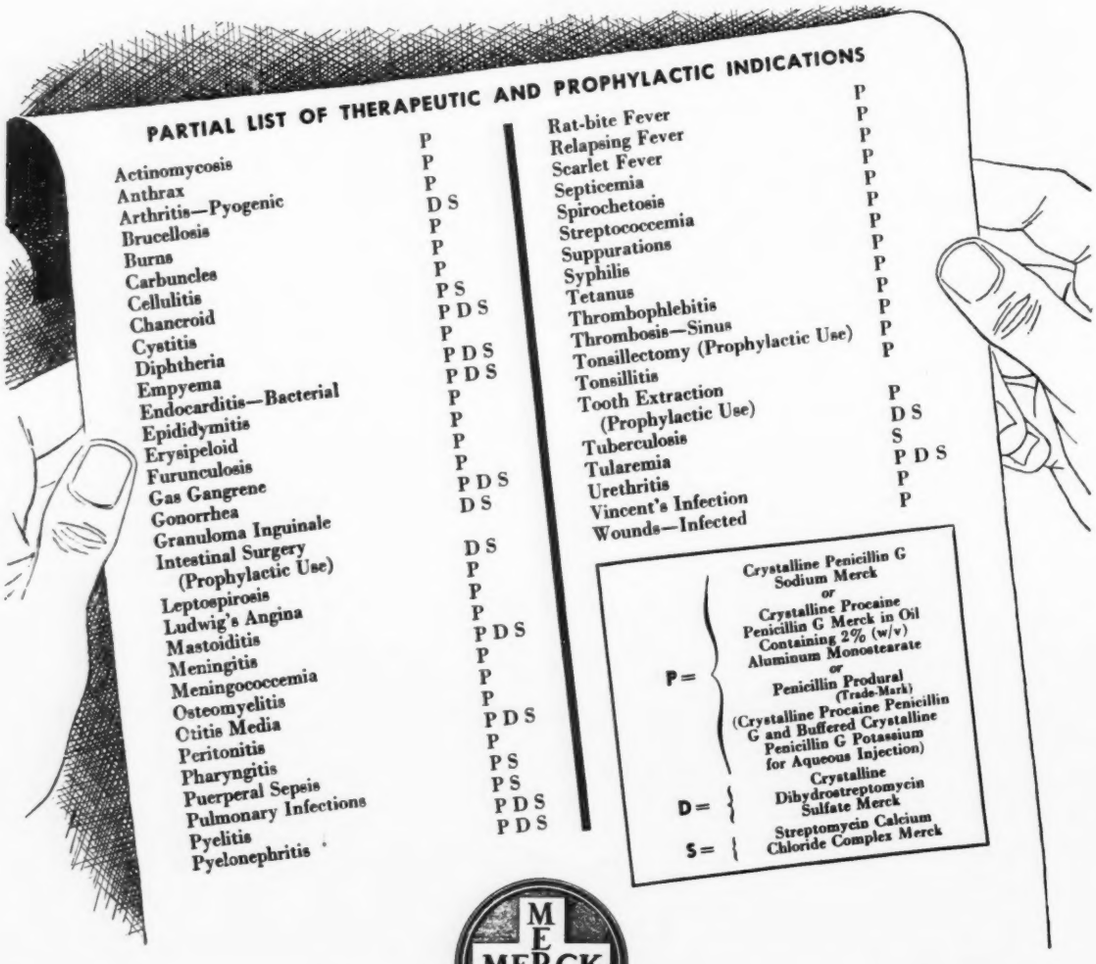

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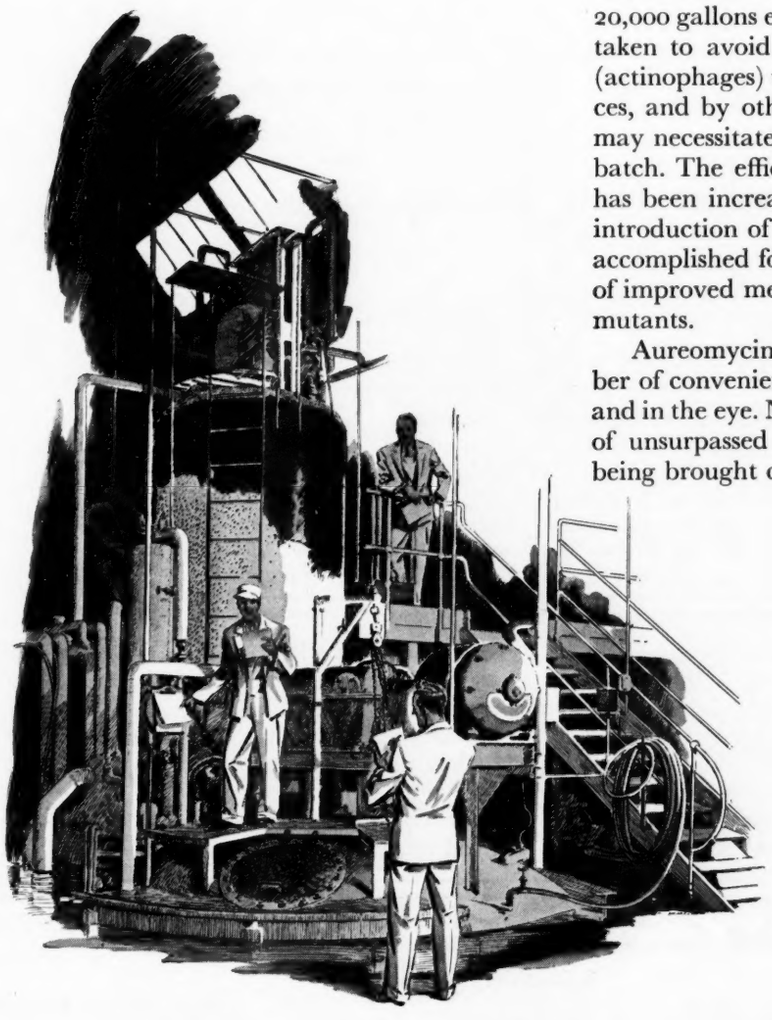

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